

THE ULTIMATE QUICK REFERENCE GUIDE
FOR CARDIOLOGISTS

OXFORD HANDBOOK OF CARDIOLOGY

EDITED BY

Punit Ramrakha | Jonathan Hill

Rapid access to essential, clinical information on the wards and in the clinic

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Oxford Handbook of Cardiology

SECOND EDITION

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Symbols and abbreviations

♂	male
♀	female
~	approximately
≈	equal to
±	plus or minus
↑	increased
↓	decreased
↔	normal
→	leading to
1°	primary
2°	secondary
°	degrees
	cross-reference
	internet reference
2D	two-dimensional
3D	three-dimensional
AAD	antiarrhythmic drug
Ab	antibody
ABG	arterial blood gas(es)
ABL	abetalipoproteinaemia
AC	attenuation correction
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
A2Ch	apical two-chamber
A3Ch	apical three-chamber
A4Ch	apical four-chamber
A5Ch	apical five-chamber
ACLS	advanced cardiac life support
ACS	acute coronary syndrome
ACT	activated clotting time
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy trial
AD	afterdepolarization
ADA	adenosine deaminase
ADMA	asymmetric-dimethyl arginine

ADP	adenosine diphosphate
AF	atrial fibrillation
AFB	acid-fast bacilli
AFL	atrial flutter
AFP	alpha-feto protein
AFCAPS/ TexCAPS	Airforce/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
A-HeFT	African-American Heart Failure Trial
AI	aortic insufficiency
AICD	automated implantable cardioverter defibrillator
AIDS	acquired immune deficiency syndrome
AIH	aortic intramural haematoma
AIIRA	angiotensin II receptor antagonist
AIRE	Acute Infarction Ramipril Efficacy
ALCAPA	anomalous left coronary artery arising from the pulmonary artery
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack
ALP	alkaline phosphatase
ALS	advanced life support
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AMP	adenosine monophosphate
ANA	antinuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
AP	anteroposterior
APC	atrial premature complex
APSAC	anistreplase
APSYS	Angina Prognosis Study in Stockholm
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARVC	arrhythmogenic right ventricular myopathy
AS	aortic stenosis
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASD	atrial septal defect
ASE	American Society of Echocardiography
ASH	asymmetric septal hypertrophy
ASIST	Atenolol Silent Ischaemia Study

AST	aspartate transaminase
AT	antithrombin
ATLAS	Assessment of Treatment with Lisinopril and Survival (study)
ATP	antitachycardia pacing
ATTR	transthyretin molecule
AV	aortic valve/atrioventricular
AVN	atrioventricular node
AVNERP	atrioventricular nodal effective refractory period
AVNRT	atrioventricular node re-entrant tachycardia
AVP	arginine vasopressin
AVR	aortic valve replacement
AVRT	atrioventricular re-entrant tachycardia
AWCL	anterograde Wenckebach cycle length
BARI	Bypass Angioplasty Revascularization Investigation
BBB	bundle branch block
BBV	blood-borne virus
BCT	broad complex tachycardia
bd	twice daily
BEAUTIFUL	Morbidity–Mortality Evaluation of Ivabradine in Patients with CAD and Left Ventricular Systolic Dysfunction
BHAT	Beta-blockers Heart Attack Trial
BHS	British Hypertension Society
BLS	basic life support
BMD	Becker’s muscular dystrophy
BMI	body mass index
BMS	bare metal stent
BNF	<i>British National Formulary</i>
BNP	B-type natriuretic protein
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BSAC	British Society for Antimicrobial Chemotherapy
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAPRICORN	Carvedilol Prospective Randomized Cumulative Trial
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (study)
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CARE-HF	Cardiac Resynchronization in Heart Failure

CARISA	Combination Assessment of Ranolazine in Stable Angina
CARMEN	Randomized controlled Multicentre Trial
CASINO	Calcium Sensitizer or Inotropic Agent or None in Low Output Heart Failure
CCB	calcium-channel blocker
CCF	congestive cardiac failure
CCS	Canadian Cardiovascular Society
CCU	coronary care unit
CEA	carcinoembryonic antigen
CFAE	complex and fractionated atrial electrogram
CFP	colour Doppler flow propagation
CHADS	Congestive heart failure, Hypertension, Age >75, Diabetes mellitus and previous Stroke)
CHARM	Candesartan in Heart Failure—Assessment of Mortality and Morbidity
CHARM-Preserved	Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction
CHB	complete heart block
CHD	coronary heart disease/congenital heart disease
CHF	congestive heart failure
CK	creatine kinase
CKD	chronic kidney disease
CIBIS	Cardiac Insufficiency Bisoprolol Study
CMR	cardiac MRI
CMV	cytomegalovirus
CNS	central nervous system
CO	cardiac output
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
COPD	chronic obstructive pulmonary disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival (study)
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial
COX-2	cyclo-oxygenase 2
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation

CPVT	catecholaminergic polymorphic ventricular tachycardia
CrCl	creatinine clearance
CREST	calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CS	coronary sinus
CT	computed tomography
CTO	chronic total occlusion
CTPA	CT pulmonary angiography
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CURRENT-OASIS7	Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention
CV	cardiovascular
CVA	cerebrovascular accident
CVC	central venous catheter
CVD	cardiovascular disease
CVP	central venous pressure (line)
CVS	cardiovascular system
CW	continuous wave
CXR	chest X-ray
DALY	disability-adjusted life year
DANAMI	Danish Acute Myocardial Infarction
DBP	diastolic blood pressure
DC	direct current
DCM	dilated cardiomyopathy
DES	drug-eluting stent
DHF	diastolic heart failure
DHP	dihydropyridine
DIC	disseminated intravascular coagulation
DIG	Digitalis Investigation Group
DM	diabetes mellitus/dermatomyositis
DMARD	disease-modifying anti-rheumatic drug
DMD	Duchenne's muscular dystrophy
DOI	dimensionless obstructive index
DVLA	Driver and Vehicle Licensing Agency
DVT	deep vein thrombosis
EBV	Epstein-Barr virus

ECG	electrocardiograph/electrocardiogram
ECHO	echocardiography
ED	erectile dysfunction
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
ELITE	Evaluation of Losartan in the Elderly
EMD	electromechanical dissociation
EMF	endomyocardial fibrosis
eNOS	endothelial nitric oxide synthase
EOA	effective orifice area
EOL	end of life
EP	electrophysiology
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EPO	erythropoietin
ERA	Estrogen Replacement and Atherosclerosis
ERI	elective replacement indicator
ERICA	Efficacy of Ranolazine in Chronic Angina
ERNV	equilibrium radionuclide ventriculography
ERO	effective regurgitant orifice
ERP	effective refractory period
ESC	European Society of Cardiology
ESM	ejection systolic murmur
ESPRIT	Estrogen in the Prevention of Reinfarction Trial
ESR	erythrocyte sedimentation rate
ET	endotracheal
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
FAME	FFR vs. Angiography for Multivessel Evaluation
FAT	focal atrial tachycardia
FBC	full blood count
FDA	Food and Drug Administration
FFP	fresh frozen plasma
FFR	fractional flow reserve
FGR	fetal growth retardation
FH	familial hyperlipidaemia/hypercholesterolaemia
FLAP	5-lipoxygenase activation protein
Fr	French gauge
FSH	facioscapulohumeral muscular dystrophy

GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GI	gastrointestinal
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio
GP	general practitioner/glycoprotein
GTN	glyceryl trinitrate
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HACEK	<i>Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella</i> spp.
Hb	haemoglobin
HbA _{1c}	glycosylated haemoglobin
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HCG	human chorionic gonadotrophin
HCM	hypertrophic cardiomyopathy
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HDU	high-dependency unit
HERS	Heart and Estrogen/Progestin Study
HF	heart failure
HFNEF	heart failure with normal ejection fraction
HFREF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
H/M	heart-to-mediastinum ratio
HOCM	hypertrophic obstructive cardiomyopathy
HOPE	Heart Outcomes Prevention Evaluation
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial
HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
HPS-THRIVE	Heart Protection Study: Treatment of HDL to Reduce the Incidence of Vascular Events
HR	heart rate
HRA	high right atrium
HRT	hormone replacement therapy
HSVB	His synchronous ventricular premature beat
HT	hypertension

IABP	intra-aortic balloon pump
IAP	incremental atrial pacing
ICD	implantable cardiac defibrillator
ICegram	intracardiac electrogram
IE	infective endocarditis
IgA	immunoglobulin A
IgG	immunoglobulin G
IGF	insulin-like growth factor
IHD	ischaemic heart disease
IJV	internal jugular vein
IM	intramuscular
IMAGE	International Multicenter Angina Exercise (study)
¹²³ I-MIBG	iodine-123-metaiodobenzylguanidine
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International trial
in.	inch
INR	international normalized ratio
IONA	Impact of Nicorandil in Angina
I-Preserved	Irbesartan in Heart Failure with Preserved Ejection Fraction
IRMER	Ionising Radiation Medical Exposure Regulations
ISR	in-stent restenosis
iu	international unit
ISIS-2	second International Study of Infarct Survival
ITU	intensive therapy unit
IV	intravenous
IVC	inferior vena cava
IVIG	intravenous immunoglobulin
IVP	incremental ventricular pacing
IVUS	intravascular ultrasound/ultrasonography
JL4	Judkins Left 4 (catheter)
JR4	Judkins Right 4 (catheter)
JUPITER	Justification for the Use of Statins in Primary Prevention
JVP	jugular venous pressure/pulse
LA	left atrium/atrial
LAA	left atrial appendage
LAD	left anterior descending (coronary artery)
LAE	left atrial enlargement
LAHB	left anterior hemiblock
LAO	left anterior oblique (projection)
LAX	long axis (view)

LBBB	left bundle branch block
LCA	left coronary artery
LCB	left coronary bypass (catheter)
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LEADERS	Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization trial
LFT	liver function test
LGMD	limb-girdle muscular dystrophy
LIFE	Losartan Intervention For Endpoint reduction
LJ	left internal jugular
LIMA	left internal mammary artery
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
LIPV	left inferior pulmonary vein
LLSE	linear least squares estimation
LMCA	left main coronary artery
LMS	left main stem (coronary artery)
LMWH	low molecular weight heparin
LPA	left pulmonary artery
Lp(a)	lipoprotein(a)
LPHB	left posterior hemiblock
LQTS	long QT syndrome
LRC-CPPT	Lipid Research Clinics Coronary Primary Prevention Trial
LSE	left sternal edge
LSPV	left superior pulmonary vein
LV	left ventricle/ventricular
LVAD	left ventricular assist device
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVF	left ventricular function/failure
LVH	left ventricular hypertrophy
LVIDd	left ventricular internal diameter in diastole
LVIDs	left ventricular internal diameter in systole
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
LVSD	left ventricular systolic dysfunction
MACE	major adverse cardiac events

MADIT	Multicenter Automatic Defibrillator Implantation Trial
MAOI	monoamine oxidase inhibitor
MARISA	Monotherapy Assessment of Ranolazine in Stable Angina
MD	muscular dystrophy
ME	mid-oesophageal
MEF2A	myocyte enhancer factor 2A
MERIT-HF	Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure
MERLIN-TIMI	Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes – Thrombolysis in Myocardial Infarction
MI	myocardial infarction
MIC	minimum inhibitory concentration
MIRACL	Myocardial Ischemia Reduction with Acute Cholesterol Lowering
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MIST	Migraine Intervention with Starflex Technology trial
MPA	main pulmonary artery
MPS	myocardial perfusion scintigraphy
MR	mitral regurgitation/modified release/magnetic resonance
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRSA	meticillin-resistant <i>Staphylococcus aureus</i>
MS	mitral stenosis
MSCT	multislice computed tomography
mSv	milli-Sievert
MUGA	multigated acquisition
MUSTT	Multicenter Unsustained Tachycardia Trial
MV	mitral valve
MVA	mitral valve area
MVD	multivessel disease
MVO ₂	myocardial oxygen consumption
MVP	mitral valve prolapse
MVR	mitral valve replacement
NaI(Tl)	sodium iodide activated by non-radioactive thallium
NBM	nil by mouth
NBTV	non-bacterial thrombotic vegetations
NCD	non-communicable disease
NCEP-ATP	National Cholesterol Education Program—Adult Treatment Panel
NCT	narrow complex tachycardia

NG	nasogastric
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
NSTEMI	non-ST-segment elevation MI
NSVT	non-sustained ventricular tachycardia
NTproBNP	N-terminal pro-B-type natriuretic hormone
NTSC	National Television Standard Committee
NVE	native valve endocarditis
NYHA	New York Heart Association
OASIS 5	Fifth Organization to Assess Strategies in Ischemic Syndromes
OCP	oral contraceptive pill
OCR	optical coherence reflectometry
OCT	optical coherence tomography
od	once daily
OM	obtuse marginal
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril
OPG	orthopentamogram
OPTIME-CHF	Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
OS	opening snap
OVG	omniflow vascular graft
PA	pulmonary artery
PAD	peripheral arterial disease/pulmonary artery diastolic
PAI	plasminogen activator inhibitor
PAL	phase alternating lines
PAN	polyarteritis nodosa
$P_a\text{CO}_2$	partial pressure of carbon dioxide in the arterial blood
$P_a\text{O}_2$	partial pressure of oxygen in the arterial blood
PARTNER	Placement of Aortic Transcatheter Valve trial
PAS	periodic acid–Schiff
PASP	pulmonary artery systolic pressure
PBMV	percutaneous balloon mitral valvuloplasty
PCI	percutaneous coronary intervention
PCI-CURE	Percutaneous Coronary Intervention—Clopidogrel in Unstable angina to prevent Recurrent Events
PCR	polymerase chain reaction

PCSK9	proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDE-5	phosphodiesterase type 5
PDGF	platelet-derived growth factor
PE	pulmonary embolism
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEFR	peak expiratory flow rate
PEP	post-exposure prophylaxis
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure
PES	paclitaxel-eluting stent
PET	positron emission tomography
PFHB	progressive familial heart block type I
PFO	patent foramen ovale
PLA	parasternal long axis
PLATO	Platelet inhibition and Patient Outcomes trial
PM	polymyositis
PMBV	percutaneous mitral balloon valvuloplasty/valvotomy
PMT	photomultiplier tube
PMV	percutaneous balloon valvuloplasty/valvotomy
PO	per os (oral)
POBA	'plain old balloon angioplasty'
PPAR- α	peroxisome proliferator-activated receptor alpha
PPI	proton pump inhibitor
PPM	patient-prosthesis mismatch
PRAGUE-2	Primary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis
PR	pulmonary regurgitation
prn	when required
PROSPECT	Predictors of Response to CRT
PROVED	Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PS	pulmonic stenosis
PSA	parasternal short axis/prostate-specific antigen
PSM	presystolic murmur
PT	prothrombin time
PTCA	percutaneous transluminal coronary angioplasty

PTH	parathyroid hormone
PTP	point-to-point
PUO	pyrexia of unknown origin
PV	pulmonary valve/pulmonary vein
PVARP	post-ventricular atrial refractory period
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
qds	four times a day
RA	right atrium/rheumatoid arthritis
RAA	right atrial appendage
RAD	right anterior descending (coronary artery)
RADIANCE	Randomized Assessment of Digoxin on Inhibitors of ACE
RALES	Randomized Aldactone Evaluation Study
RAO	right anterior oblique
RAS	renin–angiotensin system
RBBB	right bundle branch block
RCA	right coronary artery
RCT	randomized controlled trial
REVIVE	Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy
RF	rheumatic fever/rheumatoid factor/radiofrequency
RFA	radiofrequency ablation
RFV	right femoral vein
RHD	rheumatic heart disease
RIJ	right internal jugular
RIMA	right internal mammary artery
RITA	Radiofrequency Interstitial Tumour Ablation
RNP	ribonucleoprotein
ROA	regurgitant orifice area
RPA	right pulmonary artery
RR	respiratory rate
RRR	relative risk ratio
RSPV	right superior pulmonary vein
rt-PA	recombinant tissue plasminogen activator
RV	right ventricle/ventricular
RVA	right ventricular apex
RVEDP	right ventricular end-diastolic pressure
RVF	right ventricular function
RVH	right ventricular hypertrophy
RVIT	right ventricular inflow tract

RVOT	right ventricular outflow tract
RWCL	retrograde Wenckebach cycle length
4S	Scandinavian Simvastatin Survival Study
SA	sinoatrial
SAH	subarachnoid haemorrhage
SAM	systolic anterior motion
SAN	sinoatrial node
SaO ₂	arterial oxygen saturation
SAVE	Survival and Ventricular Enlargement (study)
SAX	short axis (view)
SBE	subacute bacterial endocarditis
SBP	systolic blood pressure
SC	subclavian/subcostal
SCA	Society of Cardiovascular Anesthesiologists
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SCM	sternocleidomastoid muscle
SCV	subclavian vein
SENIORS	Study of the Effect of Nebivolol Interventions on Outcomes and Rehospitalization in Seniors with Heart Failure
SES	sirolimus-eluting stent
SHBG	sex-hormone-binding globulin
SHIFT	Systolic Heart Failure Treatment with I _f Inhibitor Ivabradine Trial
SK	streptokinase
SLE	systemic lupus erythematosus
SNRT	sinus node re-entrant tachycardia
SOLVD	Studies of Left Ventricular Dysfunction
SPECT	single photon emission computed tomography
SR	slow release/sinus rhythm
SS	suprasternal
SSRI	selective serotonin reuptake inhibitor
SSS	sick sinus syndrome
STEMI	ST-segment elevation MI
STIR	short tau inversion recovery
SV	stroke volume
SVD	structural valve degeneration
SVC	superior vena cava
SVG	saphenous vein graft
SVR	systemic vascular resistance

SVT	supraventricular tachycardia
SYNTAX	Synergy between Percutaneous Coronary Intervention with Taxus and Coronary Surgery
T	tesla
$t_{1/2}$	half-time
TAPAS	Thrombus Aspiration during Percutaneous Coronary Intervention in Acute myocardial Infarction
TAVI	transcatheter aortic valve implantation
TB	tuberculosis
^{99m}Tc	technetium-99m
TC	total cholesterol
TDI	tissue Doppler imaging
TDP	torsades de pointes
tds	three times a day
TFT	thyroid function test
TG	transgastric/triglycerides
TGA	transposition of the great arteries
TGF- β	transforming growth factor-beta
TIA	transient ischaemic attack
^{201}Tl	thallium-201
TLC	therapeutic lifestyle changes
TLR	target lesion revascularization
TIBET	Total Ischaemic Burden European Trial
TID	transient ischaemic dilatation
TIMI	Thrombolysis in Myocardial Infarction
Tn	troponin
TNF- α	tumour necrosis factor alpha
TNT	Treating to New Targets
TOE	transoesophageal echocardiography
t-PA	tissue plasminogen activator
TPN	total parenteral nutrition
TPP	thiamine pyrophosphate
TR	tricuspid regurgitation
TRITON-TIMI	Trial to Access Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction
TTE	transthoracic ECHO
TV	tricuspid valve
TVI	time-velocity interval
UA	unstable angina
U&E	urea and electrolytes

UFH	unfractionated heparin
UKPDS	UK Prospective Diabetes Study
ULN	upper limit of normal
US	ultrasound
USS	ultrasound scan
VA-HIT	Department of Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial
ValHeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction Trial
3VD	three-vessel disease
VE	venous embolism
VERP	ventricular effective refractory period
VF	ventricular fibrillation
VLDL	very low-density lipoprotein
VMA	vanillyl mandelic acid
VPC	ventricular premature complex
V/Q	ventilation/perfusion
VPB	ventricular premature beats
VSD	ventricular septal defect
VT	ventricular tachycardia
VWF	von Willebrand factor
WBC	white blood cells
WCC	white cell count
WCL	Wenckebach cycle length
WHI	Women's Health Initiative
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study
WPW	Wolff–Parkinson–White (syndrome)

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Exercise ECG

A commonly used test involving a treadmill, blood pressure (BP) measurement, and continuous electrocardiograph (ECG) monitoring. Overall sensitivity for coronary heart disease is around 68% and specificity is 77%. This increases when considering prognostically significant disease, which has a sensitivity of 86%. The test improves to have a predictive accuracy of >90% in intermediate- to high-risk patients (older men with ischaemic symptoms). The test is of least value in populations that are least likely to be suffering from ischaemic heart disease; e.g. asymptomatic middle-aged women have a positive predictive value of <50%.

Indications

- Diagnosis of ischaemic heart disease (IHD): intermediate- or high-probability IHD, vasospastic angina.
- Post-myocardial infarction (MI): pre-discharge (submaximal test in days 4–7 to assess prognosis, decide upon exercise programme, and evaluate treatment), late post-discharge (symptom-limited 3–6 weeks).
- Pre- and post-revascularization.
- Evaluation of arrhythmias: optimizing rate-responsive pacemaker function, evaluation of known or suspected exercise-induced arrhythmias, and evaluation of treatment of above.

Contraindications

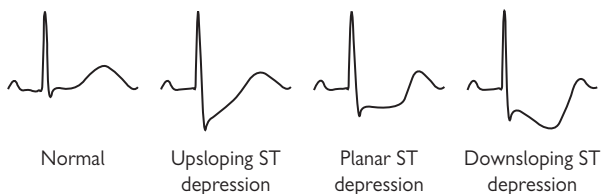
- Fever/acute viral illness.
- Myocarditis/pericarditis.
- Severe aortic stenosis.
- Aortic dissection.
- Uncontrolled hypertension.
- Overt cardiac failure.
- Unstable angina or acute phase of MI.
- Significant resting arrhythmia (e.g. uncontrolled atrial fibrillation or complete heart block).
- Known severe left main stem (LMS) or LMS equivalent disease.
- Physical disability.
- ECG abnormality rendering interpretation of ST segment difficult (e.g. left bundle branch block (LBBB), left ventricular hypertrophy (LVH) with strain or digoxin ECG changes).

When to stop

- Target heart rate achieved (tests have better sensitivity and specificity if the target heart rate is reached (>85% of 220 minus age in years for men or 210 minus age in years for women).
- Worsening angina or excessive breathlessness.
- Dizziness.
- Fatigue/patient requests to stop.
- Atrial arrhythmia other than ectopic beats.
- Frequent ventricular ectopic beats or ventricular tachycardia (VT).

- Worsening ST segment shift (elevation or depression) at least 2 mm depression but up to 5 mm depression.
- BP fall or failure to rise.
- Exaggerated hypertensive response to exercise (systolic blood pressure (SBP) >220 mmHg).
- New high-grade atrioventricular (AV) block or bundle branch block.

Criteria for a positive test



- Planar or downsloping ST depression of at least 1 mm 80 ms after the J point (junction between the QRS and ST segment).
- ST elevation.*
- Increase in QRS voltage (ischaemic left ventricular (LV) dilatation).
- Failure of BP to rise during exercise (ischaemic LV dysfunction).*
- Ventricular arrhythmias.*
- Typical ischaemic symptoms during exercise.
- Inability to increase heart rate.

***Features that are indications for urgent angiography:** Also ST depression at low workload (<<6 minutes Bruce) in multiple lead groups, persisting into recovery, >2 mm, downsloping pattern.

Causes of false-positive tests

- Cardiomyopathies.
- Hypertension.
- LVOT (left ventricular outflow tract) obstruction.
- Mitral valve prolapse syndrome.
- Hyperventilation.
- Resting ECG abnormality (LBBB, pre-excitation, digoxin).
- Electrolyte abnormalities (hypokalaemia).
- Tricyclic antidepressants.
- Syndrome X.
- Coronary artery spasm.
- Sympathetic overactivity.

National Institute for Health and Clinical Excellence (NICE) guidance 2010—chest pain of recent onset¹

Historically, exercise ECG testing has been the cornerstone of investigation of patients presenting with stable anginal chest pain. However, sensitivity and specificity are poor compared with other investigations. Recent UK guidelines discouraged the use of exercise ECG in patients without known coronary artery disease.

Instead, NICE recommended cardiac computed tomography (CT) for patients with low likelihood of significant coronary artery disease, a functional test such as dobutamine or exercise echocardiography for those with intermediate likelihood, and invasive coronary angiography for those with high likelihood.

¹ National Institute for Health and Clinical Excellence (March 2010). *Chest pain of recent onset*, <http://guidance.nice.org.uk/CG95>.

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Cardiac computed tomography

In the past decade, major advances in CT technology have enabled cardiac CT to emerge as a non-invasive alternative to conventional invasive coronary angiography.

Coronary artery calcium scoring

Calcified coronary plaque represents approximately 20% of the total coronary artery plaque burden. Therefore, the degree of coronary calcification can be used as a surrogate for coronary artery atherosclerosis. A calcium score is obtained through a low-radiation unenhanced (i.e. no iodinated contrast) scan. The degree of calcification in each coronary vessel is then expressed as a figure and summed to give the total coronary artery calcium score, commonly using the Agatston scale. A score of 0 correlates with a low risk of coronary artery disease, whereas a score of >400 correlates with high risk of significant atherosclerotic plaque burden.

Clinical studies have shown that the calcium score provides additional information for cardiovascular risk stratification above and beyond traditional factors such as age, sex, hypertension, family history, hyperlipidaemia, and diabetes.

CT coronary angiography

CT coronary angiography is performed by injecting iodinated contrast into the peripheral veins. When the level of contrast in the aorta reaches a specified level, the scan is launched and images are acquired. The images are then analysed using computer software, which allows manipulation in two dimensions and three-dimensional (3D) reconstruction of the coronary arteries and cardiac chambers, also known as 'volume rendering'.

Technical considerations

Temporal versus spatial resolution

The principal challenge to imaging the coronary arteries using CT is to achieve high temporal resolution. Temporal resolution is defined as the time taken to acquire an image. As the beating heart moves, it needs to be 'frozen' during image acquisition. Motion is greatest during systole, whereas the heart is relatively still during diastole. Images acquired during diastole are therefore most likely to be motion free, allowing accurate interpretation and diagnosis. A CT scanner must therefore be capable of acquiring images rapidly during the short diastolic phase when the heart is motionless.

Imaging small structures such as coronary arteries requires high spatial resolution. Spatial resolution is defined as the narrowest distance between two objects that can be distinguished by the detector. CT spatial resolution is determined by the voxel size (i.e. 3D pixel).

Heart-rate control

The duration of systole is relative fixed at different heart rates, but the duration of diastole varies greatly. A slow heart rate (i.e. <65 bpm (beats per minute)) is preferable, to ensure motion-free imaging of the coronary arteries.

Oral beta-blockade given 1–2 h before the scan is widely used in the United States. Alternatively, intravenous beta-blockade with serial boluses of metoprolol administered to the patient on the CT gantry has been shown to be a safe, fast, and effective method of achieving optimal heart-rate control. Premedication with two days of oral beta-blockers (to be taken the day before and on the day of the scan) is also effective and minimizes the need for administration of intravenous metoprolol at the time of the scan. Calcium-channel blockers are a practical alternative in patients with a contraindication to beta-blockers

Strategies for reducing radiation effective dose

A number of strategies have emerged to reduce the effective dose of ionizing radiation per scan:

- reduction of field of view ('carina to base of heart')
- tube voltage reduction in non-obese patients (from 120 kV down to 100 kV)
- electrocardiographically controlled tube current modulation (current is reduced in systole and increased in diastole)
- electrocardiographically controlled prospective gating (tube is only switched on at specific phase of the cardiac cycle, usually mid-diastole or 75% of the R–R interval).

By combining these techniques, the effective dose for CT coronary angiography is now approaching 1 mSv (milli-Sievert).

Sensitivity and specificity

Modern 64-slice and above CT scanners have been shown to provide excellent sensitivity (95%) and specificity (83%). As a consequence, CT coronary angiography has a very high negative predictive value (upwards of 95%). The principal clinical application of CT coronary angiography is to rule out significant coronary artery disease in patients with low to intermediate cardiovascular risk.

Clinical applications of cardiac CT

Comparison with traditional invasive coronary angiography

Traditional cardiac catheterization remains the gold standard for diagnosing coronary artery disease. It has excellent temporal and spatial resolution and allows for intervention if significant disease is identified. However, it is invasive and exposes the patient to potential vascular complications, including MI, stroke, and vascular-access complications.

With new 256- or 320-detector CT, the extended coverage and scan time of less than 0.5 s allows the entire heart to be imaged in a single heartbeat. Compared with conventional angiography, CT has a lower spatial resolution (0.4–0.6 mm vs. 0.2 mm) and temporal resolution (60–220 ms vs. 8 ms).

Comparison with functional tests

Historically, non-invasive functional tests (e.g. exercise tolerance testing, stress echocardiography, nuclear imaging, positron emission tomography (PET), perfusion magnetic resonance imaging (MRI)) have been used to select those patients deemed at intermediate risk who are likely to require invasive coronary angiography and intervention. However, many of these tests are labour intensive and not all are readily available in every hospital. In addition, the false-positive rate is substantial, leading to patients with normal coronary arteries undergoing unnecessary cardiac catheterizations.

Indications for cardiac CT

The principal role of cardiac CT in current clinical practice is to rule out or detect coronary artery disease. CT is particularly good at assessing anomalous coronary arteries and coronary artery bypass graft patency.

Additional indications

These include:

- screening for coronary artery disease (i.e. calcium scoring).
- detection of coronary artery disease in patients at low to intermediate risk.
- assessment of coronary artery bypass grafts (CABGs).
- assessment of anomalous coronary arteries.
- pulmonary vein mapping prior to electrophysiological studies/ablations.
- assessment of congenital heart disease anatomy.
- evaluation of intracoronary masses.
- evaluation of suspected aortic dissection.
- assessment of coronary stent patency.
- assessment of plaque morphology—soft/calcified/mixed.

Advantages and disadvantages of cardiac CT

Advantages

- Fast.
- Non-invasive (avoids vascular risks of invasive angiography).
- Inexpensive.
- Identifies CABG graft origin/target/patency.
- Plaque characterization—i.e. ability to assess not just the vessel lumen but also the vessel wall (soft/calcified/mixed morphology).

Disadvantages

- Ionizing radiation.
- Difficult to interpret degree of stenosis if there is significant coronary calcification.
- Difficult to see into stents and assess patency.
- Difficult to interpret degree of stenosis at CABG graft anastomosis.
- Requires regular and slow heart rates.

Future applications of cardiac CT

CT perfusion imaging

New CT techniques are now enabling integration of anatomical assessment of the coronary arteries with functional information. Intravenous contrast is injected and the myocardium is scanned repeatedly over a period of time. The first pass of contrast through a region of interest is tracked to produce tissue-specific time–density curves, which are then interpreted to determine blood flow within the tissue. However, using current CT technology, the predominant barrier to use of CT perfusion in routine clinical practice is high radiation doses.

Multimodality hybrid imaging

An alternative to CT perfusion imaging is integration of the anatomical information from CT angiography with the functional information from stress echocardiography, single photon emission computed tomography (SPECT), PET, or perfusion MRI. Clinical studies have shown that fusing functional and anatomical information increases the sensitivity and specificity when compared with each modality in isolation.

Transthoracic echocardiography

Introduction

Despite dramatic advances in new cardiac imaging technologies, echocardiography remains the most important diagnostic imaging tool in clinical practice. Since its development by Edler and Herz almost five decades ago, and routine clinical implementation a decade later, echocardiography has developed into an intuitive, comprehensible, and practical method to rapidly and repeatedly evaluate cardiac morphology and function. Competent interpretation of the echocardiographic examination first requires an understanding of the physical principles underlying the various technique modalities.

Ultrasound physics

All forms of ultrasonic imaging are based on generation of high-frequency (>1 MHz) acoustic pressure waves from a transducer comprising one or more piezoelectric crystals. Current is passed across the latter, leading to material deformation and wave transmission. The piezoelectric element also serves as a receiver, and waves returning from insonified objects (e.g. walls, valves) deform the crystal(s), which, in turn, generate a current that can be sampled over time. Because the velocity of sound is constant, object location (spatial resolution) can be determined based on the timing of the returning signal. The amplitude of the returning signal is based on the angle of incidence (surfaces perpendicular to the ultrasound beam are stronger reflectors) and the interface of acoustic impedances (greater differences such as occur in the left ventricle at the tissue–blood interface lead to greater reflectivity). Returning ultrasound information is processed for maximum image integrity and then mapped to pixels for display and storage. While many institutions continue to store images on videotape, image degradation necessarily incurred by this medium, as well as ease-of-use issues, have led to increased implementation of digital storage, primarily on dedicated file servers.

M-mode

This was the first available form of echocardiography and, while still available on modern machines, has largely disappeared from routine use in modern laboratories. M- or 'motion'-mode images depict a single line of ultrasound over time (Fig. 1.1). The information is graphic in nature and requires considerable experience for accurate interpretation. Its advantage lies in its high sampling rate (>1 kHz) and resultant ability to depict rapidly moving structures that may be of interest from a didactic or physiological perspective.

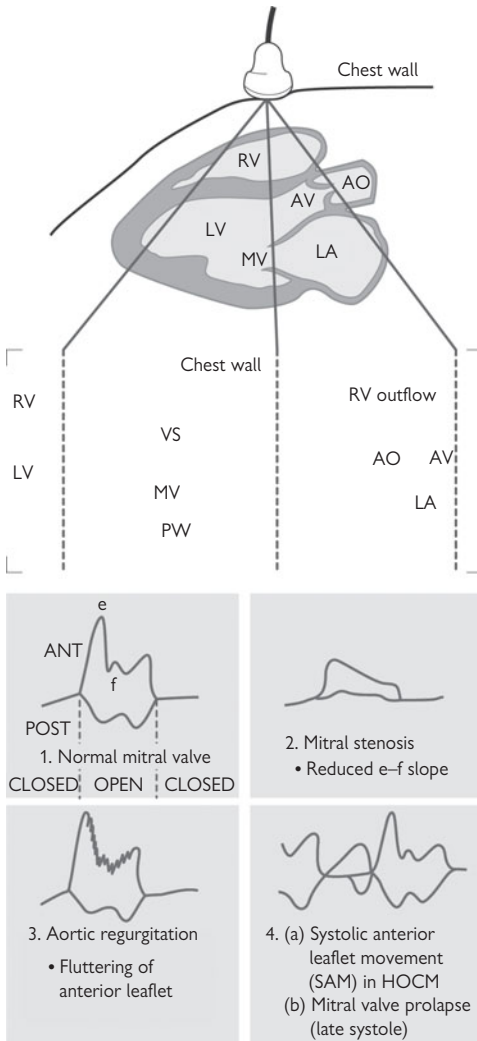


Fig. 1.1 Normal M-mode echocardiogram (AV = aortic valve; HOCM = hypertrophic obstructive cardiomyopathy; VS = interventricular septum; LA = left atrium; LV = left ventricle; MV = mitral valve; PW = posterior wall of LV; RV = right ventricle). After R Hall. *Med Int* **17**: 774. Reprinted with permission from Longmore M, Wilkinson I, Davidson E, Foulkes A, and Mafi A (2010). *Oxford Handbook of Clinical Medicine*. 8th ed. Oxford: Oxford University Press.

Two-dimensional (2D) or sector scanning (Fig. 1.2)

When an ultrasound beam is swept across a chosen cardiac window, rapid sequential sampling can be performed, leading to display of multiple 'scan lines' of information and a sector image created nearly instantaneously. Since a finite number of scan lines is possible, interpolation of data between lines is performed and an image slice or sector (hence the term 'sector scanning') is stored in digital form. Through reiterative acquisition over a cardiac cycle, a movie composed of sequentially acquired sectors is created, demonstrating structural motion, which can then be displayed on a monitor. Beam sweeping can be performed by mechanical rotation of one or more crystals, or through the use of programmed firing of a bank of crystals (phased array). Sampling rates were previously dictated and limited by videotape standards (e.g. PAL (phase alternating lines) or NTSC (National Television Standard Committee)) but, with digital capabilities appearing in some form on virtually all machines and replacing outdated tape technology, higher frame rates are possible.

The availability of harmonic tissue imaging has substantially improved image resolution by eliminating artefactual 'noise'. Low-level signals emanating from tissue and comprising the first harmonic of the transmitted ultrasound are selectively sampled. In this way, extraneous reflections such as reverberations are filtered out, leaving a cleaner image.

Three-dimensional (3D) imaging (Fig. 1.3)

While two-dimensional (2D) ECHO presents user-selected sector or tomographic information, 3D ECHO has the potential to provide a comprehensive evaluation of cardiac anatomy similar to that of more quantitatively mature technologies such as MRI or CT. Three-dimensional ECHO can be performed using the 'freehand' approach, in which multiple 2D sectors are acquired from a probe that is positionally mapped using a 'spark gap' or magnetic tracking system. Both image and position data are stored for post-hoc 3D rendering. The development of rotational and, more recently, matrix array probes, coupled to powerful computer technology, has made post-hoc, 3D chamber reconstruction a reality, with accurate volumetric assessment. Most recently, real-time rendering of spatially limited cardiac segments has been made available. There are considerable limitations, and it is currently available in limited form from various manufacturers.

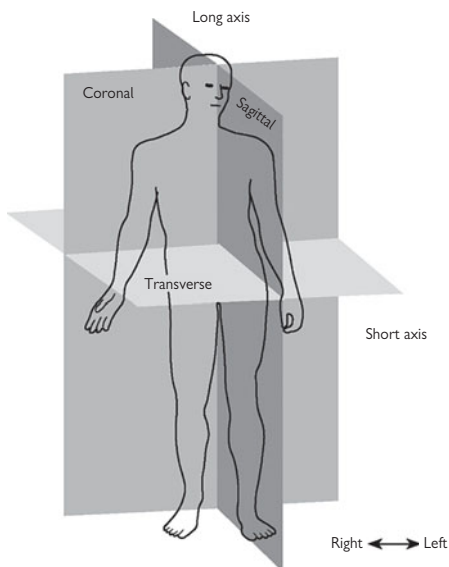


Fig. 1.2 The so-called 'anatomical position'. The subject is upright and facing the observer. Any structure within the body can be described within the references of the three orthogonal planes—two in the long axis and the third in the short axis. Reprinted with permission from Anderson RH, Ho SY, Brecker SJ (2001). Anatomic basis of cross-sectional echocardiography. *Heart* **85**: 716–20.

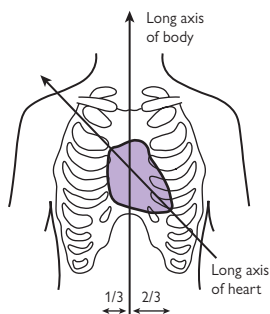


Fig. 1.3 The heart lies in the mediastinum with its own long axis tilted relative to the long axis of the body. Appreciation of this discrepancy is important in the setting of cross-sectional echocardiography. Reprinted with permission from Anderson RH, Ho SY, Brecker SJ (2001). Anatomic basis of cross-sectional echocardiography. *Heart* **85**: 716–20.

Transthoracic Doppler imaging

Quantification of object motion within the heart is performed using Doppler-based technologies. In brief, the same equipment described earlier propagates ultrasound, which is aimed at moving red blood cells or tissue.

- The frequencies of returning ultrasound are shifted upwards and downwards by cells travelling towards and away from the transducer, respectively.
- The frequency shift is proportional to an object's velocity.
- The signal intensity is dependent on the number of cells moving at a particular velocity.
- Velocity information is depicted graphically as a spectral pattern over time (similar to the M-mode display) or mapped to pixels as colour overlaying the 2D or 3D image.
- The ECHO beam must be as parallel as possible to the target, with off-axis angulation by $>30^\circ$ leading to significant underestimation of velocities.

Doppler is restricted in its ability to sample high velocities by the *Nyquist limit*, which is dependent on the sampling rate (the lower the frequency, the higher the evaluable velocity) and object depth (the deeper the object, the lower the sampling rate). When the frequency shift of moving objects (i.e. velocity) exceeds the Nyquist limit, *aliasing* occurs, precluding velocity assessment.

Pulsed Doppler permits accurate sampling of blood velocities averaged within a limited region of interest or 'sample volume'. Transducer elements serve as both transmitters and receivers, permitting selective sampling of reflected ultrasound and accurate range or spatial information. Pulsed Doppler spectral displays portray velocity vectors over time:

- *laminar flow* is found within normal vessels and chambers and characterized by a gradual increase in flow velocities from the vessel wall to the vessel centre.
- *laminar flow* is characterized by a narrow spectral trace representing a relatively discrete population of blood velocities.
- *turbulent flow* occurs across stenotic or regurgitant orifices (valves, shunts, etc.), where high-pressure gradients lead to high red-cell kinetic energy and disordered, high-velocity motion.
- *turbulent flow* is graphically portrayed as spectral broadening.
- *aliasing* often occurs with high-velocity jets, leading to 'wraparound' or the 'paint brush sign'.

Flow quantitation from pulsed Doppler

Quantitation: pulsed Doppler spectral traces can provide important information regarding flow quantitation or timing, e.g. assuming that sampling occurs at an orifice with a relatively fixed area over the cardiac cycle (e.g. the left ventricular outflow tract) by integrating the time-velocity spectral curve ('time-velocity integral' or TVI), the area under the curve can be multiplied by the area of the orifice (determined from 2D ECHO) and stroke volume determined.

Continuous wave (CW) Doppler involves continuous transmission of ultrasound with one transducer element, while a second element serves as a receiver. Higher sampling rates are achieved and, consequently, higher velocities, as found in stenotic and regurgitant lesions, can be measured. CW Doppler does not permit ranging information to be acquired and all velocities along a scan line are included in the spectral trace. CW Doppler can be performed with *stand-alone (Pedoff) probes*, where the operator determines sample location based on familiar spectral patterns.

Imaging CW Doppler permits beam steering. Transducer elements are shared for the purposes of CW and intermittent 2D imaging. A virtual cursor positioned over the 2D image can be moved to guide and minimize off-axis sampling angulation. CW Doppler velocities are depicted as a filled-in spectral tracing, since these represent sampling of all of the velocities in structures along the sampling cursor (or ultrasound beam). Blood cells travelling at the fastest velocities are represented at the outer edge of the spectral trace (peak) or darkest line of the trace (modal) velocities.

Colour Doppler flow imaging employs multigate pulsed Doppler to portray blood flow overlying the 2D image. Information is used to detect regurgitant or stenotic lesions or shunts, and qualitative assessment of velocities is possible using colour maps.

- Pixels are assigned a colour based on user-configurable mapping parameters. Pixel colour is based on average velocity in the pixel region of interest.
- By convention, the BART colour map system is used in all machines, with blue colours representing flow away from the transducer and red colour depicting flow towards the transducer (Fig. 1.4).
- The lighter the colour, the higher the velocity.
- Abnormal velocity distributions characteristic of turbulence can be mapped, usually by including a green hue ('variance mapping').
- Aliasing is depicted as a mix of colours or a 'mosaic' pattern.

Tissue Doppler imaging (TDI) is used to assess low-velocity displacement of structures. A high-pass filter excludes higher-frequency shifts caused by red-cell flow, leaving only low-velocity shifts attributable to wall motion.

- Mitral or tricuspid annular motion can be tracked and correlates with systolic and relaxation performance of the associated ventricles.
- Regional wall motion can be assessed for displacement, which may be affected by overall cardiac motion or local tethering.

Strain rate imaging can measure regional thickening and thinning, independent of the external influences described above, which influence tissue Doppler measurements. With strain rate imaging, two sampling sites are simultaneously acquired and inter-sample displacement (strain) over time (strain rate) can be determined.

Calculations from Doppler measurements

Valve gradients. The velocity of blood cells travelling across a narrow orifice is directly proportional to the pressure gradient at that point in time. This relationship is approximated by the simplified Bernoulli formula:

$$\text{Gradient (mmHg)} = 4V^2 \quad (\text{where } V = \text{peak Doppler velocity in m/s})$$

In situations where there are high flow velocities (e.g. aortic stenosis with high LVOT velocities), the flow before the stenosis must be accounted for.

$$\text{Gradient (mmHg)} = 4(V_2^2 - V_1^2) \quad (\text{where } V_2 = \text{velocity across the lesion and } V_1 = \text{pre-lesional velocity})$$

Both peak and mean gradients can be determined, the latter by integrating the velocity spectra over a cardiac cycle.

Valve area (continuity equation). This is based upon the principle that flow in the pre-valve area (e.g. LVOT) = flow across the valve. It is generally used for aortic stenosis quantitation, though it is applicable to other stenotic orifices as well.

$$\text{LVOT flow} = \text{LVOT area} \times \text{LVOT TVI by pulsed Doppler}$$

$$\text{LVOT area} = \pi (\text{maximum LVOT diameter in PLA view})^2$$

$$\text{Aortic valve flow} = \text{aortic valve area} \times \text{aortic valve TVI by CW Doppler}$$

As aortic valve flow = LVOT flow,

$$\text{Aortic valve area} = \text{LVOT TVI} / \text{aortic valve TVI} \times \text{LVOT area}$$

PLA = parasternal long axis.

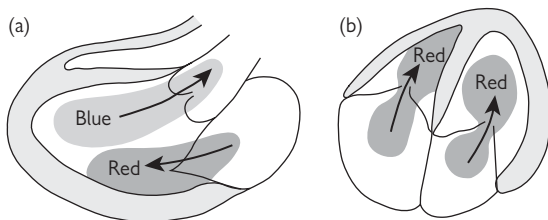


Fig. 1.4 Colour Doppler (Red: toward flow; Blue: away flow). Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12:884–900.

The standard transthoracic ECHO

Most laboratories employ imaging protocols incorporating acquisition of images from standard windows, resulting in standard views presented in a fairly standard sequence. Image quality is maximized by avoiding pulmonary artefacts and rib reflections. Pulsed and colour flow Doppler are performed following 2D imaging in each view. Standard ECHO windows and views include:

Left parasternal window

- *Long axis (PLA)* (Fig. 1.5): left atrium, ventricle, proximal ascending aorta, mitral and aortic valves, and right ventricle.
- *Short axis (PSA)* (Fig. 1.5): four levels—aortic valve/left atrial level: includes the tricuspid and pulmonic valves and pulmonary artery; mitral valve, papillary muscle, and apex.
- *Right ventricular inflow tract (RVIT)*.
- *Right ventricular outflow tract (RVOT)*.

Apical window

- *4 chamber (A4Ch)*: atria, ventricles and AV valves, media, septal, and anterolateral LV walls.
- *5 chamber (A5Ch)*: A4Ch angled anteriorly to the LVOT.
- *2 chamber (A2Ch)*: anterior and inferior LV walls.
- *3 chamber/apical long axis (A3Ch)*: apical version of PLA view with the anteroseptal, posterior walls, and LVOT.
- *Suprasternal window (SS)*: aortic arch.
- *Subcostal window (SC)*: 4 chamber, short axis, inferior vena cava.
- *Suprasternal window (optional)*: aortic arch and proximal descending thoracic aorta.
- *Right parasternal window (optional)*: ascending aorta and CW Doppler of the aortic valve.

Chamber evaluation

- Chambers are routinely measured from M-mode tracings or, preferably, using digital calipers to perform point-to-point (PTP) assessment from 2D images.
- Area tracings provide enhanced accuracy but are time-consuming.
- Volumes are derived from 2D and PTP analysis using geometric modelling. The most common volumetric approaches include the modified Simpson's biplane method of stacked discs, bullet and area-length formulae.
- 3D volume assessment has been validated but the technology is immature and inappropriate for routine clinical assessment.
- Most clinical labs perform PTP measurements online. End-diastole is usually defined as the beginning of the QRS complex, and end-systolic measurements are performed at maximum LV contraction.

The standard transthoracic ECHO: continued

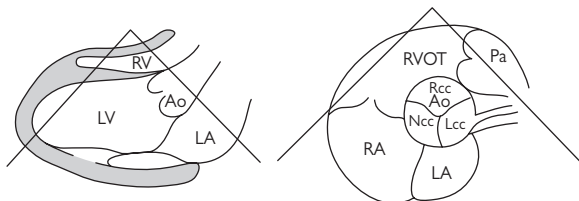


Fig. 1.5 (a) Parasternal long axis view; (b) Parasternal short axis view (aortic level). Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12:884–900.

Left atrium

- Measure at ventricular end-systole (minimum LV chamber dimension).
- Linear (anteroposterior) from PLA view at aortic cusp level (A4Ch).
- Area (A4Ch) and volume (preferably modified Simpson's formula).

Left ventricle

- Measure at end-diastole and end-systole.
- Linear from PLA at mitral tips in end-diastole/systole.
- Septal wall thickness from PLA at mitral tips in end-diastole.
- Posterior wall thickness.
- Volumes (modified Simpson's biplane method of discs).
- Derived variables:
 - *fractional shortening*: $LVIDd - LVIDs / LVIDs$ where LVID = LV internal diameter in diastole (d) and systole (s).
 - *ejection fraction* (from 2D- or 3D-generated volumes or derived from M-mode (e.g. Teicholz formula)).
 - *mass*: can be derived from M-mode measures (American Society of Echocardiography (ASE)-modified Penn formula), 2D volumetric models, or 3D reconstruction. M-mode mass calculations tend to over-quantify LV mass.

Aortic root and ascending aorta

Linear measurements from 2D PLA view or M-mode. The root is measured at cuspal level, and the aorta is measured at the sinotubular junction and 2 cm above this.

Right atrium

- Area from 2D A4Ch view.
- Inferior/superior and lateral/medial PTP measurements.

Right ventricle

- PTP measurements are exclusively used.
- Irregularity of chamber configuration makes standardized quantitation difficult.

Pulmonary artery

PTP medial–lateral measurement in PSA at aortic valve level.

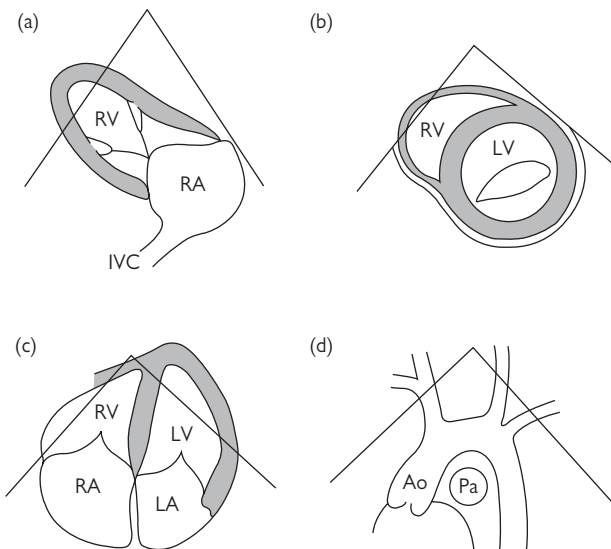


Fig. 1.6 (a) Parasternal long-axis view (RV inflow); (b) parasternal short-axis (mitral valve level); (c) apical 4-chamber view; (d) suprasternal long axis. Ao = aorta; IVC = inferior vena cava; Pa = pulmonary artery. Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12:884–900.

Assessment of wall motion

Assessment is based upon review of multiple cuts as described earlier. In general, abnormalities of LV regional function should be apparent in more than one view. Various labelling systems have been used but the American Heart Association (AHA) Cardiac Imaging Committee 17-segment model is the standard convention:

- *basal* (6): anteroseptal, anterior, anterolateral, posterolateral, inferior, inferoseptal.
- *mid LV* (6): same as above.
- *apical* (5): anterior, lateral inferior, septal, and true apical. See Fig. 1.7.

Regional functional assessment

- Systolic function should be classified as 'normal', 'globally hypokinetic', or demonstrating the presence of 'regional wall motion abnormalities'.
- Global hypokinesis is consistent with cardiomyopathy, either ischaemic or non-ischaemic. Some degree of regional variation may be present in non-ischaemic cardiomyopathy.
- The presence of distinct regional wall motion abnormalities with large areas of normal regional function is suggestive of underlying coronary artery disease.
- Evaluation should ideally be based on the degree of regional thickening as opposed to endocardial motion. Unfortunately, this is not always possible.
- Each regional segment can be qualified as:
 - hyperkinetic.
 - normal.
 - hypokinetic.
 - akinetic.
 - dyskinetic.
- Wall motion quantification, based on similar characteristics, may be prognostically useful, but is not useful in routine evaluation.
- Identification of hyper-echogenic, thinned areas suggests the presence of scarring and should be mentioned in the evaluation.
- Scarred segments may demonstrate endocardial motion, without wall thickening, due to tethering by peripheral segments.

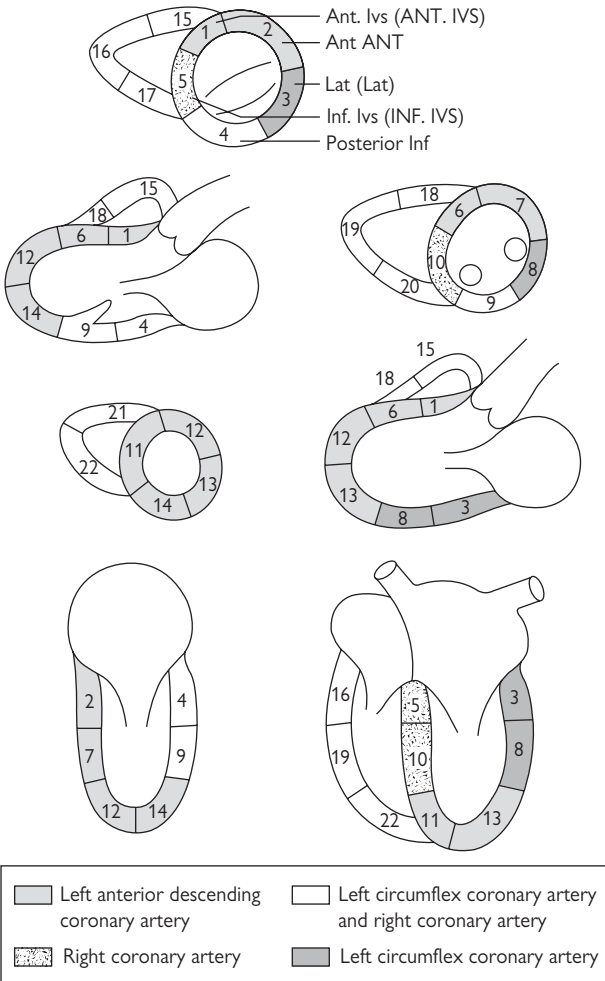


Fig. 1.7 American Heart Association 17-segment model. From Swanton H (2003) *Pocket Consultant: Cardiology*, 5th ed, Oxford: Blackwell Publishing.

Assessment of LV systolic function

Global functional assessment

- Ejection fraction estimation is usually performed qualitatively. Echocardiographers need to routinely 'recalibrate' their assessment abilities by comparing qualitative readings to more accurate quantitative modalities, such as MRI, radionuclide ventriculography, 3D or even quantitative 2D ECHO (see Table 1.1).
- 2D ECHO ejection fractions can be quantified most efficiently on or offline by the:
 - Simpson's modified biplane method of stacked discs*: A4Ch and A2Ch LV traces are performed and the apex–annulus length is divided into a standard number of equal segments, the length of which serves as disc height. Cross-sectional disc area is calculated from the elliptical formula ($\pi r_1 r_2$) where r_1 and r_2 = the endocardial medial–lateral dimension of each segment in the A4Ch and A2Ch views, respectively.
 - cylinder hemi-ellipsoid model*: volume is determined by measuring the LV endocardial area (A) on the PSA view at the papillary muscle level and the longest apex–annulus length (L) in any apical view. Volume = $5/6AL$.

Table 1.1 Assessment of left ventricular ejection fraction

LV ejection fraction	Qualitative assessment
>75%	Hyperdynamic
55–75%	Normal
40–54%	Mildly reduced
30–39%	Moderately reduced
<30%	Severely reduced


- LV stroke volume*: integration of LVOT spectra \times LVOT area (derived from diameter in PLA view).
- Systemic output*: LV stroke volume \times heart rate.
- Pulmonary stroke volume*: integration of pulmonary artery spectral trace \times pulmonary artery area (derived from systolic medial–lateral dimension at the level of Doppler sampling).
- RV output*: pulmonary stroke volume \times heart rate.
- Pulmonic/systemic shunt ratio (Qp/Qs): pulmonary output/systemic output.
- Tissue Doppler of mitral and tricuspid annular motion.

Essential aspects of ECHO assessment in patients with impaired LV systolic function

Anatomy

- LV dimensions (systolic and end diastolic).
- LV ejection fraction.
- Regional wall motion abnormalities.

Doppler characteristics

- E:A ratio (grade according to Fig. 1.7  Assessment of LV diastolic function, p. 27).
- E deceleration time.
- Estimate pulmonary artery (PA) systolic (from tricuspid regurgitation (TR) jet).
- Estimate PA diastolic (from pulmonary regurgitation (PR) jet).
- Estimate pulmonary capacitance (= stroke volume/(PAs – PAd pressures)).

Implications for therapy

- Mitral regurgitation at end diastole if AV delay too long.
- Dys-synchrony (TDI septum/lateral annulus >60 ms).

Assessment of LV diastolic function

Evaluation of LV diastolic function includes measurement of the various phases of diastole including isovolumic relaxation, early filling, diastasis (atrioventricular pressure equilibration without LV filling), and atrial systole. These measures are generally age and heart-rate dependent, and affected by LV loading conditions to variable degrees (see Fig. 1.8).

Pulsed Doppler mitral inflow: E wave (peak early diastolic velocity), A wave (peak atrial systolic velocity), E/A ratio and transmitral deceleration time. The following should be taken into account when assessing these parameters:

- E/A ratio is particularly dependent on sample volume placement (annulus, mitral tips, etc.) and loading conditions.
- E/A ratio decreases with age, and assessment must be age-normalized. An E/A ratio <1.0 is common among the elderly and often represents normal aging.
- increasing LV filling pressures (e.g. in heart failure) lead to 'pseudonormalization' of the ratio, which often reverts to an abnormal pattern following manoeuvres to reduce LV preload (e.g. diuresis) or Valsalva manoeuvre.
- the deceleration time correlates somewhat with invasive measures of LV stiffness, whereas other measures largely reflect LV relaxation.

Pulsed Doppler of pulmonary veins: Flow into the left atrium can be sampled. S, D, and A waves represent systolic and diastolic atrial filling. The A wave is generated by reverse flow into the pulmonary veins during atrial contraction.

- The S/D ratio increases with age, as LV diastolic relaxation declines. A pulmonary vein A wave duration more than 30 ms greater than transmitral A wave duration suggests elevated LV filling pressure.

CW Doppler of LV outflow/mitral inflow: Isovolumic relaxation time.


Tissue Doppler of medial and lateral mitral annuli (E', A')

- This is considered the least load-dependent filling variable. There is generally poor correlation between medial and lateral velocities, with the lateral annulus measurement being more reproducible.
- The E/E' ratio correlates roughly with LV end-diastolic pressure; a ratio >15 is strongly suggestive of elevated filling pressure, and a ratio <8 strongly suggestive of normal filling pressure.

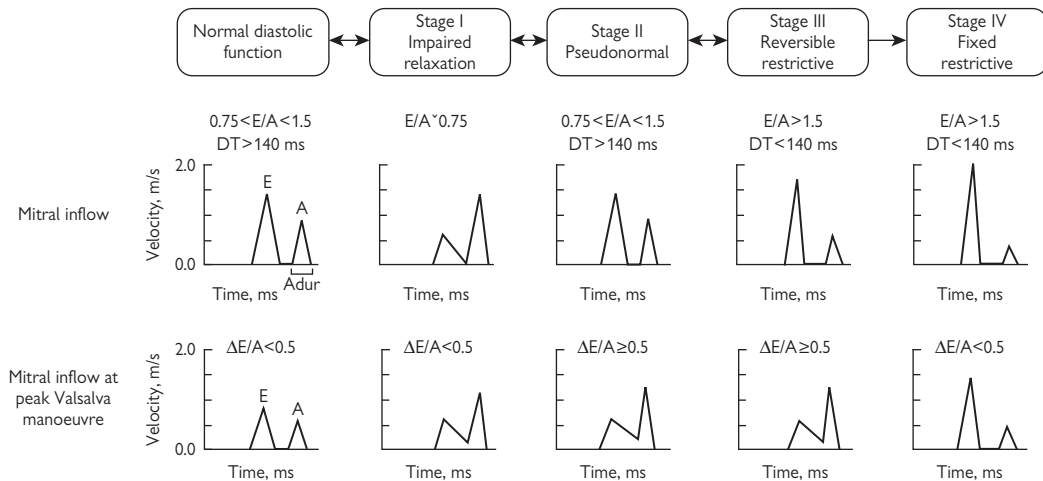
Colour Doppler flow propagation (CFP) slope: Rate of blood acceleration into the LV from the annulus to the apex.

Various diastolic profiles combining some of the above parameters have been suggested as indicators of degree or stage of 'diastolic dysfunction'. (see Fig. 1.8). In general:

- markers of impaired relaxation (e.g. decreased E and E' are accompanied by compensatory enhancement of A and A'), reduced pulmonary venous D, and reduced CFP slope.

- increases in LV filling pressure lead to pseudonormalization of the transmitral Doppler E/A ratio, with less effect on Doppler with Valsalva manoeuvre and tissue Doppler velocity ratios.
- as compliance decreases or a patient's position on the LV pressure–volume curve advances (operating stiffness), the transmitral DT drops below 130 ms, early Doppler filling velocity is increased, and, due to elevated late diastolic LV pressures, atrial contraction and associated velocities are reduced.
- if E/E' ratio <8 and LA is of normal size, symptoms are unlikely to be due to diastolic heart failure.
- do not miss constriction (see  Constrictive pericarditis vs. restrictive myocardial disease, p. 475); look for:
 - septal 'bounce' and dys-synchrony.
 - inferior vena cava (IVC) dilatation.
 - hepatic vein expiratory reversal.

Echocardiographic classification of diastolic dysfunction



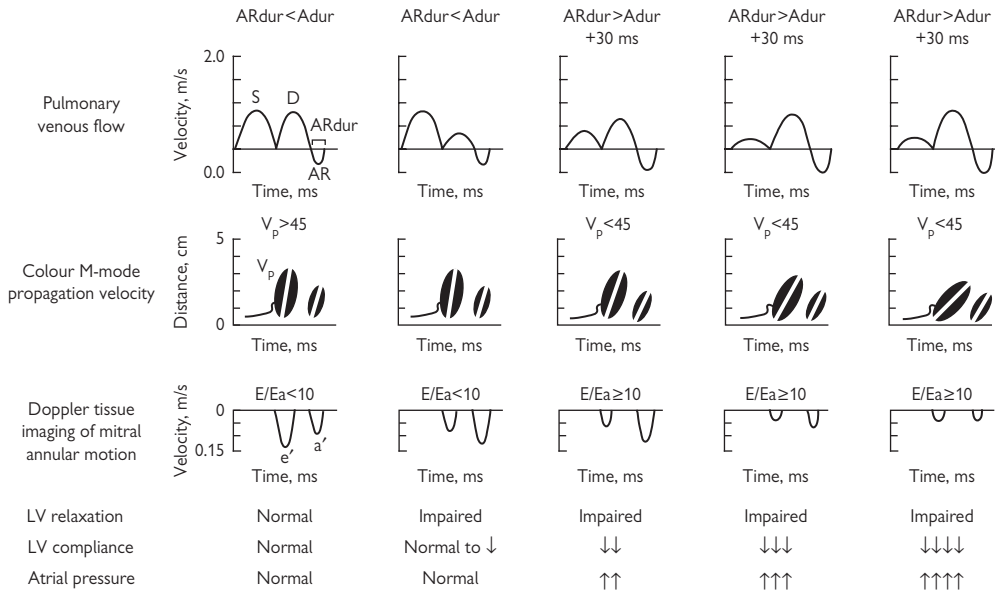


Fig. 1.8 Echocardiographic classification of diastolic dysfunction. Reproduced with permission from *Journal of the American College of Cardiology*, Vol 48, No.3, 2006. August 1, 2006:e1–148. Bonow et al, AHA/ACC Best Practice Guidelines.

Echocardiography in aortic stenosis

Aetiology

- Aortic stenosis (AS) can be congenital or, more commonly, degenerative. In late stages, severe fibrocalcification precludes aetiologic identification, even on direct intraoperative visualization. Chronic severe AS is usually accompanied by concentric LV hypertrophy, a product of pressure overload.
- *Bicuspid aortic valve* is diagnosed best on short-axis view and can display various configurations. Often a 'raphe' is observed, representing the undeveloped commissure where persistent cuspal fusion is present. Systolic cuspal 'doming' is consistent with congenital AS.
- *Degenerative AS* is typically initiated in the annulus fibrosus (most commonly in the non-coronary cusp area) and gradually proceeds to invade the cuspal bases, body, and, in later stages, the tips. Valve thickening without haemodynamic stenosis is often termed 'sclerosis'.

Haemodynamics

- Stenosis is defined as a haemodynamically significant reduction in valve area as indicated by a rise in transvalvular pressure gradient.
- Pressure gradient is dependent upon flow and, in the setting of low cardiac output, may be minimally elevated despite significant stenosis.
- Valve area is generally not indexed to body size in most clinical labs, and categorization of severity may vary. One convention is as follows:
 - *mild*: area $>1.5 \text{ cm}^2$ and $<2.0 \text{ cm}^2$.
 - *moderate*: >1.0 and $<1.5 \text{ cm}^2$.
 - *severe*: $<1.0 \text{ cm}^2$.
 - *critical*: $<0.7 \text{ cm}^2$.

ECHO diagnosis

- Assess cuspal separation or presence of doming. A trileaflet valve with one cusp opening fully (approaching edge of the root) is probably not stenotic.
- CW Doppler-derived gradients are reported as an instantaneous peak and/or mean. The mean gradient is more reliable in determining stenosis severity.
- Catheterization lab gradients are 'peak to peak', with pressure measurements that are usually not acquired simultaneously and often do not correlate with Doppler gradients.
- Peak transvalvular velocity $>2.5 \text{ m/s}$ (instantaneous gradient of 25 mmHg) suggests some degree of stenosis.
- Elevated cardiac output or significant aortic regurgitation will increase transvalvular flow and gradient but not valve area.
- *The dimensionless obstructive index (DOI)* is the ratio of LV outflow tract velocity (pulsed Doppler)/transvalvular velocity (CW Doppler), and takes into account elevated flow. General guidelines:
 - *DOI* $<50\%$: significant stenosis.
 - *DOI* $30\text{--}50\%$: moderate stenosis.
 - *DOI* $<30\%$: severe stenosis.

Aortic valve area is quantitated by the continuity equation. The most common errors in this assessment include:

- under-measurement of the LVOT.
- failure to assess LVOT Doppler at an angle within 30° of the flow vector.

Transoesophageal echocardiography

Clinical indications

Transoesophageal echocardiography (TOE) is a semi-invasive test that has advantages over transthoracic ECHO (TTE). The TOE transducer is closer to the heart and has a higher frequency (5 MHz), thus giving better resolution than TTE (2.5 MHz). The oesophageal approach means that an unobstructed ECHO window is possible in those patients with poor transthoracic windows, and it also allows the use of TOE in the intra-operative setting without interfering with the operative field. Virtually all TOE probes have multiplane scanning capability.

See Fig. 1.9.

Patient preparation

The procedure is performed using local anaesthesia and, if required, intravenous (IV) sedation.

Prior to procedure

- The patient is fasted for 4 hours.
- Any dentures are removed and the back of the throat is sprayed with lidocaine (Xylocaine®), taking care not to exceed the maximum dose because absorption of the local anaesthetic can cause systemic effects (nausea, drowsiness, and ataxia).
- IV midazolam (dose 2–6 mg) can be given for sedation, but in the majority of patients, local anaesthesia will suffice.
- Flumazenil may be required to reverse the effect of midazolam.

Procedure

- Oxygen and wall suction should be available. A nurse should be available to assist in monitoring during and after the procedure. A bite guard is used.
- The patient is placed in the left lateral position with the neck flexed. Oxygen saturation and the ECG are monitored.
- The sheathed TOE probe is lubricated with gel and introduced gently to the pharynx. Once the patient swallows, the probe is advanced into the oesophagus. The patient should be told that the initial gag feeling will ease with the passage of the probe from the pharynx into the oesophagus. Undue force must be avoided.

Post-procedure

- The patient should be 'nil by mouth' for 1 h post-procedure, for the effect of the local anaesthetic to wear off. Some patients such as paediatric or adolescent patients with complex congenital heart disease will require general anaesthesia.

Pitfalls

- Serious complications are rare (0.2%) and the mortality rate is less than 0.01%. Serious complications include oesophageal rupture, laryngospasm, ventricular arrhythmia, and severe hypoxia.

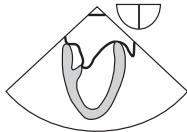
- The proximal aortic arch and the upper portion of the ascending aorta is a 'blind spot' because of the interposition of the trachea and right bronchus between the heart and oesophagus, and dissection could be missed. Due to the resolution of TOE, certain normal structures e.g. Chiari network, aortic valve strands, prosthetic valve sutures, might be inadvertently mistaken as pathology.

Indications for transoesophageal echocardiography

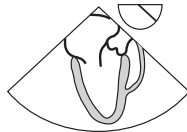
- Valve disease:
 - mitral valve prolapse, assess mitral stenosis for mitral valvuloplasty.
 - aortic regurgitation, adjunct to assess aortic stenosis.
 - Prosthetic valve dysfunction.
- Bacterial endocarditis.
- Cardiac source of embolism, including patent foramen ovale (PFO).
- Aortic pathology:
 - acute aortic dissection, aortic rupture and aortic aneurysm, atheroma.
- Prior to DC cardioversion.
- Cardiac masses.
- Pericardial disease and masses.
- Congenital heart defects.
- Intraoperative monitoring of valve procedures, LV and RV function.
- Intensive therapy unit (ITU) setting to determine cause of haemodynamic collapse.
- Guiding interventional procedure—atrial septal defect (ASD) closure, mitral valvuloplasty.
- Poor transthoracic window.



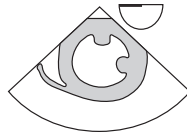
(a) ME four chamber



(b) ME two chamber



(c) ME LAX



(d) TG mid SAX



(e) TG two chamber



(f) TG basal SAX



(g) ME mitral commissural



(h) ME ME AV SAX



(i) ME AV LEX



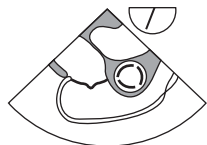
(j) TG LAX



(k) Deep TG LAX



(l) ME bicaval



(m) ME RV inflow-outflow



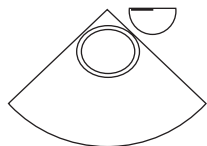
(n) TG RV inflow



(o) ME asc aortic SAX



(p) ME asc aortic LAX



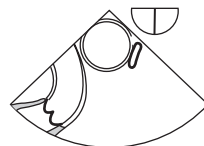
(q) Desc aortic SAX



(r) Desc aortic LAX



(s) UE aortic arch LAX



(t) UE aortic arch SAX

Fig. 1.9 Standard TOE views: AV, aortic valve; LAX, long axis; ME, mid oesophageal; RV, right ventricular. SAX, short axis; TG, transgastric. Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12: 884–900.

TOE for a cardiac source of embolism

Patients who have suffered a cerebral embolic event, especially at a young age (<50 years), may have a cardiac source of emboli that is not evident on TTE. Once a TTE has excluded major causes such as mitral valve disease, a TOE should be performed to examine the following:

Key views

- Left atrial clot or spontaneous contrast (0° ME (mid-oesophageal) four chamber, 90° ME bicaval).
- Left atrial appendage for clot (90° ME two chamber).
- Patent foramen ovale (90° ME bicaval).
- Atrial septal aneurysm (90° ME bicaval).
- Atrial myxoma (0° ME four chamber, 90° ME two chamber, 90° ME bicaval).
- LV cavity for left ventricular thrombus, including apex (120° TG long axis (LAX)).
- Aortic atheroma (>4 to 5 mm, mobile and ulcerated aortic plaques have the highest risk of embolization) in the ascending arch and descending aorta.
- Aortic and mitral valves for vegetations.

Diagnosis of patent foramen ovale

- 10 ml of saline is agitated by injecting between two syringes connected by a three-way tap. Some operators report better opacification with colloid (e.g. Haemaccel®) rather than saline.
- Position the TOE probe at either 0° or 180° at mid-oesophagus level to visualize the right atrium.
- Inject agitated saline.
- Repeat with Valsalva manoeuvre induced by asking the patient to cough, or try to blow out the plunger from a 2 ml syringe.
- The presence of bubbles in the left heart chamber's three cardiac cycles after opacification of the right atrium is required for a diagnosis of PFO.
- Sensitivity of detection of R–L shunt can be improved by injecting into the femoral vein rather than an antecubital vein, but this is not routinely done.

Diagnosis of atrial septal aneurysm

- The base of the aneurysm should measure at least 1.5 cm.
- The excursion of the membrane should be at least 1.5 cm in the direction of either atrium.

TOE in aortic dissection

TOE can demonstrate the presence of an intimal flap in the aorta with great accuracy (sensitivity of 99%, specificity 98%). TOE should examine the following:

Key views

- Presence of intimal flap in:
 - ascending aorta (120° ME aortic valve (AV) LAX, 0° ME ascending aortic short axis (SAX)).
 - descending aorta (0° descending aortic SAX, 90° descending aortic LAX).
 - aortic arch (0° UE aortic arch LAX, 90° UE aortic arch SAX).
- Coronary artery involvement (0° ME AV SAX).
- Aortic valve for regurgitation, annular diameter, cusp (120° ME AV LAX).
- Site of intimal rupture, colour flow mapping to determine true and false lumen.
- Aortic rupture with collection around the aorta and pericardial effusion.
- Thrombus or spontaneous contrast in false lumen.

Blood pressure control should be initiated prior to TOE, and sedation should generally be given to avoid undue hypertension.

Pitfalls

- Blind spots in the proximal arch.
- Aortic artefacts are especially common in dilated aorta—artefacts are characterized by their position parallel to the aortic wall, blood flow velocities similar on either side of the artefact, and superimposition of the colour flow map over the artefact.
- An equivocal TOE examination should prompt the use of another imaging modality such as CT or MRI.

Aortic intramural haematoma (AIH)

This appears as an area of wall thickness >7 mm with or without the presence of an echolucent space in the aortic wall. It may be difficult to distinguish this entity from an atherosclerotic plaque or penetrating aortic ulcer, and other imaging modalities may be required.

Diagnosis of AIH

- ≥ 7 mm crescent or circular thickening of the aortic wall.
- Extending 1–20 cm longitudinal.
- No intimal flap or Doppler flow in thickened aortic wall.

TOE in endocarditis

TOE is more sensitive (sensitivity >90%) than TTE for the detection of vegetations (sensitivity <60%) in infective endocarditis (IE), especially if the vegetations are <5 mm in size.

TOE is the investigation of choice in:

- patients with poor TTE window.
- prosthetic valve endocarditis.
- high or intermediate suspicion of IE with negative TTE.
- detection of IE-related complications.

Some authorities feel that all patients with IE should have TOE for early detection of complications such as aortic abscess formation, and for *Staphylococcus aureus* IE, where the risk of complications is high. Note that negative TTE and TOE has a negative predictive value of 95%. If clinical suspicion remains high, *TOE should be repeated in 7–10 days*.

Echocardiographic criteria for diagnosis of IE according to Duke classification

- Vegetations.
- Abscess formation: most commonly occurs in the aortic root followed by the ventricular septum, mitral valve, and papillary muscle. TOE has a sensitivity of 80% compared to TTE, which is 30%.
- Prosthetic valve dehiscence.

OR

- New valvular regurgitation.

Other complications include: leaflet perforation, fistula, and chordal rupture.

Key views

- Aortic root abscess seen (60° ME AV SAX).
- Mitral valve views (see  TOE for mitral regurgitation, p. 38).
- Tricuspid valve (0° ME four chamber, 120° TG LAX).
- Pulmonary valve (90° ME RV inflow–outflow).

TOE is useful prior to surgery to exclude infection on other valves and to look for abscess formation that will require additional procedures.

Pitfalls

Valve strands (Lambli's excrescences), chordal structures from myxomatous degeneration, and non-specific valvular thickening may be mistaken as vegetations, leading to a false-positive TOE result.

Echocardiographic features requiring surgical referral

- Acute aortic or mitral regurgitation causing left ventricular failure. There may be associated valve destruction such as perforation or chordal rupture.
- Prosthetic valve dehiscence causing haemodynamic compromise.
- Large abscess formation or extension of abscess despite antibiotics.
- Vegetations—recurrent embolization.
- High risk of embolic events for mitral valve vegetation >10 mm.
- Increase in vegetation size after 4 weeks of antibiotics.

TOE for mitral regurgitation (MR)

- Morphological assessment of mitral valve to determine mechanism of regurgitation:
 - elongation or rupture of chordae.
 - retraction of chord.
 - prolapse or restriction of leaflets.
 - subvalvular apparatus.
 - annular diameter, degree of calcification.
 - LV size and regional wall abnormalities.

Key views (see Fig. 1.10)

- Leaflet prolapse or restriction (0° ME four chamber, 45° ME mitral commissural, 90° ME two chamber, 120° ME LAX).
- Annular diameter (120° ME LAX).
- Leaflet prolapse (0° TG basal SAX).
- Subvalvular apparatus (90° TG two chamber).

How to assess severity of MR using TOE

- Length of regurgitant jet.
- Timing of MR: early systolic vs. holosystolic by colour M-mode.
- Direction of jet: eccentric wall hugging or central.
- Pulmonary venous flow (see Table 1.2).
- Other features of severe MR:
 - regurgitant jet width at its origin, ≥ 0.5 cm in 120° view, so-called 'vena contracta'.
 - active volume-loaded LV.
 - Peak E-wave velocity >1.5 m/s.

Table 1.2 Assessment of severity of MR using pulmonary venous flow

Grade	Length (MR jet/LA size)	Timing	Direction	Pulmonary venous flow
1	1/3	Early	Central	Normal
2	2/3	<Pansystolic	Central	Normal
3	2/3	Pansystolic	Eccentric	Normal or reversed
4	3/3	Pansystolic	Eccentric or central	Reversed

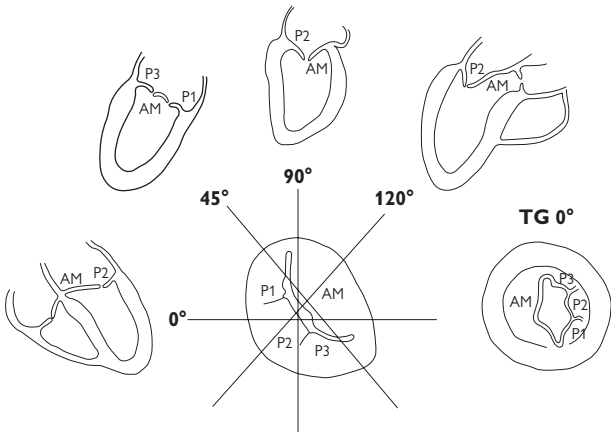


Fig. 1.10 Assessment of the mitral valve by TOE. Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12: 884–900.

TOE for mitral valve prolapse

Mitral valve prolapse (MVP) causes eccentric mitral regurgitation, hence prolapse of the posterior leaflet produces anteriorly directed jet and vice versa. Note that when the MR jet hugs the wall of the left atrium, the reported severity should be upgraded. The left and right pulmonary veins should be sampled with pulse wave to check for systolic flow reversal.

Classical MVP

- At least 2 mm displacement of the mitral leaflet beyond the mitral annular plane in any view.
- Mitral valve thickness >5 mm.

Non-classical MVP

- The prolapsing leaflets are not thickened (<5 mm) and are unaffected by myxomatous degeneration.
- Such patients are not at increased risk of complications such as severe MR, infective endocarditis, and sudden death as compared to the classical form of MVP.

TOE for mitral valve repair

- Mapping of the prolapsing mitral valve segments can be performed to aid surgical planning.
- Two-thirds of cases of MVP involve the middle scallop of the posterior leaflet, and 70% of these cases can be successfully repaired.
- Ruptured chordae and flail mitral valve leaflets should be noted.
- The mitral annulus diameter is also measured (upper limit normal is 35 mm), and the presence of annular calcification noted.


TOE in chronic ischaemic MR

- Typically, the mitral valve is structurally normal and therefore MR is termed 'functional'.
- Remodelling of the LV displaces the papillary muscle towards the apex, and traction on the mitral leaflets causes incomplete leaflet closure.
- The zone of coaptation is displaced towards the apex, and 'systolic tenting' of the mitral valve is seen.
- LV remodelling and dilatation appears to be necessary for severe MR to develop. Isolated segmental wall motion abnormalities without LV dilatation are not generally associated with severe MR.
- Annular dilatation will exacerbate incomplete leaflet coaptation but does not, in isolation, cause MR.
- In the presence of an inferior or posterior infarct, the posterobasal wall (site of the posteromedial papillary) of the LV may become aneurysmal. This can exert asymmetrical traction on the chordae, resulting in retraction of the posterior leaflet. There is abnormal apposition, and an eccentric, anteriorly directed, jet of MR results.

Key views

- Restriction of leaflet, systolic tenting of MV (0° ME four chamber, 45° ME mitral commissural, 90° ME two chamber, 120° ME LAX)
- Annulus size (120° ME LAX).
- LV assessment, especially the posterobasal wall (90° ME two chamber, 0° TG mid SAX).

TOE for mitral stenosis

Assessment for suitability for percutaneous balloon mitral valvuloplasty (PBMV see  Mitral regurgitation, p. 158):

- LA and left atrial appendage (LAA) thrombus—relative contraindication.
- grade 2 MR—relative contraindication.
- mitral valve anatomy:
 - mobility.
 - thickening.
 - calcification.
 - subvalvular thickening.

TOE for assessment of cardiac masses

- *Normal anatomy that should not be mistaken for pathology:* Chiari network, eustachian valve near the inferior vena cava, trabeculations in the left atrial appendage, ridge separating the left pulmonary vein and left atrial appendage.
- Myxomas are the most common primary cardiac tumour (50% of all tumours), and specific features can be delineated on TOE:
 - attached by a stalk to the interatrial septum near the fossa ovalis in 90% of cases.
 - 75% are in the LA.
 - may have a speckled, cystic appearance with frond-like projections.
 - may be multiple. If they occur elsewhere, they may be mistaken for thrombus (tend to be homogeneous in appearance) or other tumours.
 - may cause valve obstruction.
- Fibroelastomas are benign tumours that attach to valve apparatus. They have a frond-like appearance and may mimic vegetations or myxoma.
- Primary malignant cardiac tumours and secondary metastatic disease can infiltrate the epicardium, myocardium, or endocardium, or present as intracavity mass.
- Pericardial involvement in malignant disease frequently causes pericardial effusion.

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TOE assessment of mitral valve prosthesis

TOE is especially sensitive in detecting MR in association with a prosthetic valve, because the left atrium is imaged in the foreground and is therefore devoid of the artefacts generated by the metal elements of the prosthetic valve.

Paraprosthetic mitral leak

The sewing ring of the mechanical prosthetic valve appears as a bright ring attached to the mitral annulus. If a significant circumference of the sewing ring has come away (e.g. from endocarditis), a rocking movement of the valve will be evident—this 'rocking prosthetic valve' is characteristic of a partial dehiscence of the valve.

Key views

The mitral valve sewing ring should be identified in and interrogated with colour flow and CW Doppler:

- 0° ME four chamber.
- 90° ME two chamber.
- 120° ME LAX views of the mitral valve.

The motion of the prosthetic valve mechanism (e.g. tilting disc) should be assessed to ensure the discs or occluder are moving freely in 120° ME LAX view.

The presence of flow outside the sewing ring (i.e. paraprosthetic) is not normal, although small or mild jets may be seen early after valve implantation. This represents failure of the sutures attaching the valve ring to the annulus, either from technical failure or from the effect of endocarditis. Paraprosthetic leaks are more likely in the presence of a calcified mitral annulus.

Transprosthetic mitral leak

Mechanical prosthetic valves have regurgitation during closure of the valve, which arises within the sewing ring (i.e. intraprosthetic). These 'closing jets' are a normal feature and should not be mistaken as pathological. In general they can be easily distinguished from pathological regurgitation (see Table 1.3). Causes for abnormal intraprosthetic leak include pannus or thrombus preventing the occluder from functioning properly.

Tissue mitral prosthesis

This should be assessed in the same way as a mechanical prosthesis. The prosthetic valve leaflet should be assessed for:

- prolapsing leaflet.
- flail leaflet.
- thickened cusps (>3 mm—higher risk of dysfunction).
- the Doppler signal for a flail cusp shows a characteristic striated 'zebra-stripe pattern'.

Obstruction of the prosthetic mitral valve

This may be due to thrombus or pannus formation. The diagnosis is made by finding:

- limited movement of the occluder or disc.
- haemodynamic confirmation by finding a high peak pressure gradient across the mitral valve (>2.5 m/s) or a prolonged pressure half-time ($t_{1/2} >200$ ms).

Features of normal closing jets

- Short jets <3 cm length.
- Narrow base <5 mm.
- Early systolic rather than pansystolic leak.

Table 1.3 Upper limit of pressure half-time (ms) for commonly used valves

Valve type	Maximum $t_{1/2}$ (ms)
Starr-Edwards [®]	170
St Jude [®]	131
CarboMedics [®]	117
Carpentier-Edwards [®]	171
Native valve	60

TOE for aortic valve prosthesis

- The orientation of the aortic valve means that the sewing ring will obstruct the view of the orifice of the valve for mechanical and stented tissue aortic valves. Thus, assessment of aortic paraprosthetic leak on 2D imaging is limited compared to mitral valve assessment.
- CW interrogation is not possible because the LVOT is orientated perpendicular to the ultrasound beam, when the aortic valve is assessed from the standard ME views.
- A combined TTE and TOE approach is required, because TTE is ideally suited to Doppler interrogation of the aortic valve.

Deep transgastric view

A deep transgastric TOE allows imaging of the aortic valve in the foreground, and allows proper alignment of the Doppler signal from the aortic valve (0° deep TG LAX and 120° TG LAX views). This view is useful to assess:

- movement of the aortic prosthetic valve mechanism.
- colour flow Doppler interrogation for aortic regurgitation.
- CW assessment of aortic regurgitation.
- CW measurement of the aortic valve gradient.

The use of the deep transgastric TOE view is especially useful for assessment of aortic prosthetic valve function when a mechanical mitral prosthesis is also present. This is because acoustic shadowing from the mitral valve obscures the LVOT in all ME TOE views of the aortic valve. However, this view is not possible in all patients.

Regurgitation is most commonly transprosthetic in aortic tissue valves. The following may be visible on TOE: cusp thickening (>3 mm predicts risk of valve failure), cusp tear, cusp prolapse, and flail cusp. Rocking of the aortic prosthesis is due to dehiscence of the valve (40% circumference affected) and best seen in the 0° ME AV SAX and 120° ME AV LAX views.

Key views

The aortic valve prosthesis is assessed in:

- 0° ME AV SAX.
- 120° ME AV LAX.
- 0° deep TG LAX.
- 120° TG LAX.

TOE assessment of normal and dysfunctional aortic prosthetic valves

Normal peak gradient across mechanical aortic valve prosthesis

- St Jude Medical.[®] ● 24 ± 7 mmHg.
- Medtronic Hall.[®] ● 21 ± 7 mmHg.

Significant stenosis or obstruction likely in mechanical aortic valve

- Peak velocity of >4 m/s or mean velocity of 3 m/s are suggestive of obstruction.

Tissue aortic valves

- Aortic valve area by continuity equation <1 cm².
- Mean gradient >26 mmHg.
- Ratio of LVOT to peak velocity across aortic valve <0.2 .

Stentless aortic valves

- (Freestyle[®] or Toronto[®] valve) or aortic homografts do not have the disadvantage of a sewing ring casting an acoustic shadow on the aortic valve orifice, and TEE gives excellent views of valve cusps. Some of these valves are indistinguishable from native valves on TOE.

Intraoperative TOE

Indications

AHA class I indications

- Cardiac valve repair.
- Haemodynamic compromise where LV function is unknown.
- Complex endocarditis surgery where perivalvular extension is suspected.
- Complex valve replacement such as homograft valve replacement with coronary reimplantation.
- Ascending aortic dissection with aortic valve involvement.
- Posterior or loculated pericardial effusion.
- Congenital heart surgery.
- Hypertrophic obstructive cardiomyopathy (HOCM surgery).

AHA class II indications

- Heart valve replacement.
- Cardiac tumour removal.
- Coronary surgery including 'off pump bypass'.
- Cardiac aneurysm repair.
- LV or RV assist device implantation.
- Ascending aortic dissection without aortic valve involvement.
- Cardiac trauma.
- Intracardiac thrombectomy or pulmonary embolectomy.
- Heart and/or lung transplantation to assess anastomotic sites.

Key views (see Fig. 1.11)

LV assessment is made on these views:

- 0° ME four chamber.
- 90° ME two chamber.
- 120° ME LAX.
- 0° TG mid SAX.

TOE in the intraoperative and perioperative period (in ITU) to assess haemodynamic instability

- Coronary artery bypass graft failure: examine LV in all 3 coronary distributions. The transgastric view shows all 3 coronary distributions in one view.
- Hypovolaemia: reduced LV cavity size and end-systolic cavity obliteration is a sign of hypovolaemia.
- Pericardial collection: any collection can be localized to, say, just the left atrium and need not be a global collection.
- Severe LV dysfunction.
- Right ventricular failure.
- Unsuspected severe mitral regurgitation.
- Unsuspected aortic dissection.

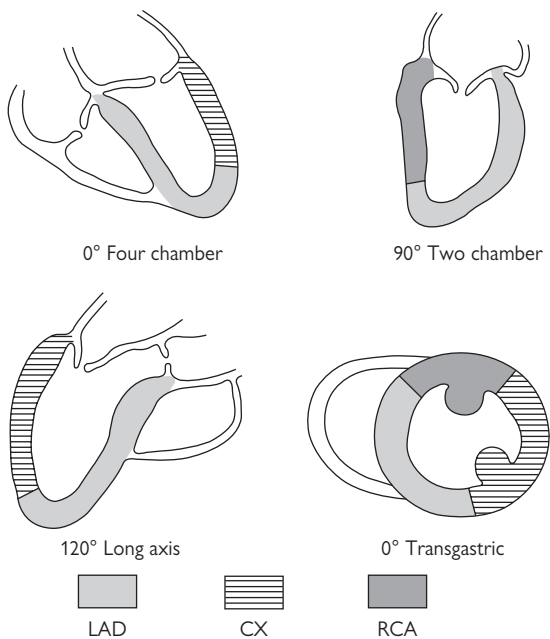


Fig. 1.11 Assessment of LV function by TOE. CX = circumflex; LAD = left anterior descending artery; RCA = right coronary artery. Reproduced with permission from Shanewise JS. *Journal of the American Society Echocardiography* 1999;12: 884–900.

Basic principles of nuclear cardiology

Nuclear medicine investigations involve the injection of a tracer (radiopharmaceutical) labelled with a radionuclide which emits gamma (or X-ray) photons. This is distributed within the body according to its chemical properties. This distribution can be imaged by single photon emission computed tomography (SPECT) using an Anger gamma camera. The most commonly performed nuclear cardiology investigation is myocardial perfusion scintigraphy (MPS), which provides physiological information in known or suspected coronary disease. Radionuclide ventriculography is an accurate method for quantifying left ventricular function, although it is now performed less commonly than in the past. Cardiac iodine-123-metaiodobenzylguanidine (^{123}I -MIBG) imaging is increasingly used to assess sympathetic innervation in heart failure. Cardiac positron emission tomography (PET) imaging is less widely available than SPECT and uses different imaging equipment and radiopharmaceuticals, but provides similar information.

The Anger gamma camera

Crystal

The key component of a gamma camera is a large flat circular or rectangular sodium iodide crystal, activated by non-radioactive thallium—NaI(Tl). The crystal is a 'scintillator', i.e. absorption of a gamma photon via the photoelectric effect yields a burst of photons of visible light within 1 mm of the interaction.

Photomultiplier tubes

The side of the crystal away from the patient is viewed by a hexagonal array of up to 100 photomultiplier tubes (PMTs). These convert the weak signal carried by photons of visible light leaving the crystal, into a detectable electrical pulse. The pattern of activation of PMTs signals the location of the originating scintillation event, with the largest electrical pulse being generated in the PMT closest to the event.

Collimator

The side of the crystal facing the patient is shielded by a collimator, a lead disc penetrated by thousands of uniform parallel channels separated by thin septa. Only photons travelling perpendicular to the collimator can penetrate the channels and enter the crystal, while the remainder are absorbed by the lead septa. Thus gamma-photons originating from a particular area of the heart can only enter a selected area of the NaI(Tl) crystal, maintaining spatial information.

SPECT image acquisition and display

Planar acquisition

Acquisition and summation of scintillations by the head of a gamma camera for a few minutes yields a planar scan, which represents the 3D distribution of radiopharmaceutical within a patient as a 2D image.

SPECT acquisition

SPECT imaging involves the acquisition of a series of planar projections at different angles as the head(s) of the gamma camera orbit(s) the patient. A dual-headed camera is preferred, with the heads positioned at 90° to one another to halve acquisition time. A typical MPS acquisition might involve 64 projections (32 per head) acquired over a 180° orbit and taking 16 minutes.

Filtered back-projection or iterative reconstruction is used to produce a set of transaxial sections through the patient. The transaxial slices can then be reorientated to the axes of the heart to produce vertical long-axis, horizontal long-axis, and short-axis slices. The count density of each pixel within the reorientated slices is displayed relative to the pixel of maximal counts in the myocardium (0–100%), using a grey scale or colour spectrum. Stress slices are displayed above corresponding rest slices to facilitate comparison.

Gated SPECT

SPECT acquisitions can be 'gated' to the ECG. The R–R interval is divided into 8 or 16 frames, and each planar projection is acquired as 8 or 16 corresponding images. Each frame is reconstructed and reorientated separately to produce SPECT slices that represent the left ventricle at a particular point in the cardiac cycle. Static slices to assess perfusion can be obtained from the same acquisition, by summing the frames for each planar projection.

Gated slices can be viewed in a looped cine format to assess regional function in terms of wall excursion and thickening. Commercially available software is used to fit endocardial and epicardial boundaries and determine end-diastolic volume, end-systolic volume, and ejection fraction.

Attenuation correction

Gamma photons emitted from the heart are variably attenuated by soft tissue. This can produce spurious apparent perfusion abnormalities in the processed slices (attenuation artefacts). Many modern gamma cameras allow attenuation correction (AC). A *transmission* acquisition is performed using one or more scanning gadolinium sources or X-ray CT, and an attenuation map is reconstructed. This is used to correct the *emission* acquisition, which is acquired simultaneously (gadolinium approach) or separately (CT approach).

Myocardial perfusion scintigraphy: technical

Overview

At rest, myocardial perfusion distal to a flow-limiting coronary stenosis usually remains normal due to progressive arteriolar dilatation. During cardiac stress, there is less vasodilator reserve available, and perfusion will be lower than that downstream of an unobstructed vessel.

A radiopharmaceutical perfusion tracer is injected during cardiac stress, and is taken up and retained by cardiac myocytes in relation to blood flow. Subsequent SPECT imaging is performed, and the distribution of radio-nuclide reflects myocardial viability and perfusion at the time of tracer injection, i.e. during stress. A separate imaging study is performed after injection of tracer at rest (technetium-99m-labelled tracers) or following redistribution of the stress injection (thallium-201), and the distribution of radionuclide primarily reflects viability.

Cardiac stress

Dynamic exercise stress (treadmill or bicycle) is the most physiological form of stress and provides important clinical information that may complement imaging findings. Many patients referred for myocardial perfusion scintigraphy (MPS) are unable to exercise to their target heart rate, and pharmacological methods are required. The drugs used fall into two categories:

- primary vasodilators (dipyridamole or adenosine): first choice, unless contraindicated by airways disease or unpaced heart block.
- inotrope (dobutamine).

Adenosine causes direct coronary vasodilatation via A_{2a} -receptors. Dipyridamole acts indirectly, increasing endogenous adenosine by inhibiting its breakdown and reuptake. Dobutamine, a synthetic beta-agonist, increases myocardial oxygen demand, causing secondary coronary vasodilatation.

Radiopharmaceutical perfusion tracers

The MPS perfusion tracers in routine clinical use are thallium-201 (^{201}Tl) and the newer technetium-99m ($^{99\text{m}}\text{Tc}$)-based tracers, sestamibi and tetrofosmin.

Thallium-201

^{201}Tl , given as thallos chloride, is a cyclotron-generated isotope. It enters myocytes down the electrochemical gradient in a similar way to potassium. Following injection at peak stress, it gradually equilibrates between the intracellular and intravascular compartments, and so immediate imaging is required. Redistribution imaging is performed 4 hours later, to assess perfusion at rest. For optimal assessment of myocardial viability, ^{201}Tl is sometimes reinjected at rest.

Technetium-99m-labelled tracers

^{99m}Tc is produced from a generator and is complexed with an organic molecule (sestamibi or tetrofosmin). ^{99m}Tc -sestamibi and ^{99m}Tc -tetrofosmin diffuse passively into myocytes, where they bind to mitochondria. The absence of significant redistribution means that imaging can be performed conveniently 30–60 minutes after injection, but separate injections are required during stress and at rest. A 2-day or a 1-day protocol may be used. A nitrate may be given prior to the resting injection, to maximize uptake into viable myocardium.

Comparison of tracers

^{201}Tl is a superior perfusion tracer physiologically, but the ^{99m}Tc agents have several practical advantages. The images produced are of higher quality because the photons are of higher energy, and can be gated to allow assessment of left ventricular function. In addition, the shorter half-life (6 hours vs. 73 hours) reduces the radiation exposure to the patient.

Myocardial perfusion scintigraphy: clinical

Indications

- Diagnostic and prognostic assessment in suspected coronary disease when exercise ECG is likely to be unreliable:
 - women.
 - patients unable to exercise adequately.
 - patients with significantly abnormal resting ECG.
- Guidance of management in known coronary disease:
 - post myocardial infarction.
 - post coronary angiography.
 - post coronary revascularization.
- Assessment of myocardial viability, ischaemia, and function in ischaemic left ventricular dysfunction.

Image interpretation

- Perfusion defects:
 - fixed (on both stress and rest acquisitions): suggests scar following myocardial infarction.
 - reversible (on stress acquisition only): suggests inducible hypoperfusion of viable myocardium distal to flow-limiting coronary stenosis.
 - Characterized by location (coronary territory), extent, and severity (prognostic importance).
 - may need to be distinguished from artefacts, e.g. anterior soft tissue attenuation in women, inferior attenuation in men.
- Other high-risk findings, e.g.:
 - increased lung uptake of ^{201}Tl .
 - transient ischaemic dilatation (TID): left ventricular cavity larger post-stress than at rest.
- Left ventricular function on gated acquisitions.

Clinical value of MPS

Diagnosis or exclusion of obstructive coronary disease¹

For the detection of angiographic coronary stenoses, the sensitivity of MPS is approximately 90%. The specificity is usually lower at approximately 75%, but may have been underestimated due to overinterpretation of artefacts and post-test referral bias. In practice, a more meaningful alternative to specificity is the normalcy rate (proportion of normal tests in a low-probability population), and this is typically 90% or more.

Prognosis

MPS is a functional test, and hence cannot predict angiographic coronary anatomy with perfect accuracy. Nevertheless, MPS provides robust prognostic information that is independent of clinical, exercise, and even angiographic data.

¹ Underwood SR, Anagnostopoulos C, Cerqueira M, et al. (2004). Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* **31**: 261–91.

- Normal MPS study predicts the annual rate of cardiac death or non-fatal MI of approximately 0.6%.²
- Low risk persists for up to 5 years in patients without known coronary disease, though this 'warranty period' is shorter in patients with diabetes and those with known coronary disease.³
- The risk associated with an abnormal study increases in proportion to the degree of abnormality.⁴
- Cardiac death is primarily a function of left ventricular ejection fraction, while non-fatal MI is mainly predicted by the extent of inducible hypoperfusion.⁵
- The prognostic benefit from revascularization may be limited to patients with inducible hypoperfusion amounting to >10% of the left ventricular myocardium.⁶

Ischaemic left ventricular dysfunction

MPS is of value in the assessment of patients with ischaemic left ventricular dysfunction to define the extent of hibernating myocardium, which has the potential to recover function following revascularization.⁷

Hibernating myocardium is:

- viable (tracer uptake >50–60% maximum counts on resting study), but
- dysfunctional at rest (hypokinetic or akinetic on gated study), with
- exhausted vasodilator reserve (inducible hypoperfusion).

2 Iskander S, Iskandrian AE (1998). Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* **32**: 57–62.

3 Hachamovitch R, Hayes S, Friedman JD, et al (2003). Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans. What is the warranty period of a normal scan? *J Am Coll Cardiol* **41**: 1329–40.

4 Hachamovitch R, Berman DS, Kiat H, et al (1996). Exercise myocardial perfusion SPECT in patients without known coronary artery disease: Incremental prognostic value and use in risk stratification. *Circulation* **93**: 905–14.

5 Sharir T, Germano G, Kang X, et al (2001). Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med* **42**: 831–7.

6 Hachamovitch R, Hayes SW, Friedman JD, et al (2003). Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* **107**: 2900–6.

7 Bax JJ, van der Wall EE, Harbinson M (2004). Radionuclide techniques for the assessment of myocardial viability and hibernation. *Heart* **90**(suppl V): v26–33.

Other nuclear cardiology investigations

Radionuclide ventriculography

Equilibrium radionuclide ventriculography (ERNV) was the first reliable non-invasive method of assessing left ventricular function.

The blood-pool is labelled with ^{99m}Tc -pertechnetate. A gated planar acquisition is obtained in a left anterior oblique projection, to minimize overlap of the left ventricle by other cardiac chambers. Regions of interest are drawn around the left ventricular cavity in end-diastole and end-systole, together with an adjacent background region of interest, allowing calculation of the ejection fraction. This counts-based method makes no assumptions about left ventricular geometry, and the ejection fraction is accurate and reproducible (+5%).

The growth of echocardiography has led to a sharp decline in the number of ERNV studies performed, but it may still be used when a reproducible technique is required for serial assessment of left ventricular ejection fraction (e.g. during chemotherapy).

Cardiac ^{123}I -MIBG imaging

Cardiac MIBG imaging is sometimes performed as a prognostic assessment in patients with left ventricular dysfunction.

MIBG is a false neurotransmitter, and is taken up by sympathetic nerve endings in the heart via the sodium- and energy-dependent 'uptake-1' mechanism. It is labelled with cyclotron-generated ^{123}I . Following injection, planar acquisitions are obtained in an anterior projection at 15 minutes and 4 hours. The overall cardiac uptake of ^{123}I -MIBG can be quantified as the heart-to-mediastinum (H/M) ratio.

Reduced H/M ratio (e.g. <1.60 on delayed acquisition) with increased washout from early to delayed imaging is an independent predictor of an adverse prognosis. It has been suggested that this might find a role in the selection of patients for implantable defibrillators.

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Positron emission tomography scanning

Radiopharmaceuticals used in PET emit positrons ('anti-electrons'), which annihilate within a short distance by combining with an electron. This produces two 511 keV gamma-photons travelling in opposite directions. A PET camera consists of a series of circular or hexagonal arrays of scintillation detectors. If each of a pair of detectors simultaneously registers a scintillation event (coincidence), positron annihilation is assumed to have occurred along a line between the two detectors (coincidence detection). Coincidence detection is used to construct transaxial slices, which can be reorientated as in SPECT.

PET allows quantitative assessment of various aspects of cardiac function in different regions of the heart:

- global and regional left ventricular function
- myocardial blood flow
- myocardial metabolism: glucose and fatty acid metabolism; myocardial oxygen consumption
- pharmacology: beta-adrenergic and muscarinic receptors; sympathetic innervation; myocardial angiotensin-converting enzyme (ACE) and angiotensin II receptors
- myocardial gene expression.

Clinical applications

Identification of myocardial viability

The main clinical application of PET scanning has been determination of the *myocardial viability* of patients with impaired left ventricular function secondary to coronary artery disease, who may benefit from surgical or percutaneous coronary revascularization. These studies have demonstrated that PET imaging has high sensitivity for predicting recovery of contractile function after revascularization, and have also provided major insights into the mechanisms underlying left ventricular dysfunction in patients with coronary artery disease.

Research applications

The large variety of compounds available for study using PET permits interrogation of many facets of cardiac function, providing important *in vivo* mechanistic information in human disease. These measurements also allow for analysis of the mechanisms underlying the benefit of established and novel therapeutic strategies. Examples include:

- myocardial blood flow and microvascular function: ischaemic heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, aortic stenosis, syndrome X.
- myocardial metabolism and cardiac energetics: ischaemic cardiomyopathy, dilated cardiomyopathy.
- cardiac autonomic function: hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, autonomic neuropathy, long QT syndrome.

Comparison of PET over conventional cardiac nuclear modalities (gamma camera, SPECT)

Advantages

- Short half-life of radionuclides.
- Better spatial resolution.
- Accurate attenuation correction allowing absolute quantification of radiopharmaceutical concentration.
- On-site cyclotron.

Disadvantages

- Expensive.
- Limited access.
- Predominantly a research application.

Adapted with permission from de Silva R and Camici PG (1994). Role of positron emission tomography in the investigation of human coronary circulatory function. *Cardiovasc Res* **28**(11): 1595–612.

Basic principles of cardiac MRI

- Cardiac MRI (CMR) is a highly versatile modality that enables cardiac structure and function to be characterized with high spatial resolution and in any plane, without using ionizing radiation.
- The patient is placed within a strong static magnetic field, 1.5–3 Tesla (T) in strength. This forces all the protons in the patient to align with the field and precess at a frequency determined by the field strength.
- A radiofrequency pulse is delivered at this resonant frequency, causing the magnetization of the protons to be flipped away from the longitudinal direction. As it decays back towards the relaxed state, radiofrequency energy is emitted by the protons.
- The relaxation times for the recovery of longitudinal magnetization and the decay of transverse magnetization are influenced by the local environment of the protons.
- The resulting signals are used to construct an image. Different sequences of pulses and varying magnetic field gradients can be used to emphasize different tissue characteristics or highlight particular anatomical details.
- Tissues that lack protons, e.g. the air-filled lung, are not well imaged by CMR in health.

Major indications for CMR include:

- evaluation of ventricular function (gold standard).
- cardiomyopathy assessment.
- assessment of ischaemia and myocardial viability.
- assessment of cardiac iron status.
- evaluation of congenital heart disease.
- evaluation of valvular heart disease.
- diagnosis and serial follow-up of aortic disease.
- assessment of pericardial disease and cardiac masses.

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Making CMR requests

- As with any other imaging modality, provide as much information as possible about the clinical question that is to be answered by the scan. The versatility of MRI provides the operator with a gamut of sequences and techniques that can be applied. A detailed clinical question will help to facilitate the construction of an appropriate imaging protocol.
- Assess for absolute contraindications prior to making a request, and detail any concerns or doubts in the referral letter (see below).
- Cardiomyopathy and ischaemia assessments are greatly facilitated by providing a resting ECG with the referral.
- Requests to assess potential hypertrophic cardiomyopathy should detail any possible alternative causes for hypertrophy, and in particular the severity, chronicity, and control of hypertension.
- When requesting viability studies, provide details of any interventions, angiogram findings, or graft details if available, as this can greatly facilitate reporting.
- For valve studies, provide any available ECHO data.
- Ask patients to bring along a favourite music CD as this can be played during the scan to minimize anxiety. Claustrophobic patients in particular benefit from this.
- Where language may be a barrier, ensure that someone able to interpret attends the scan, or provide warning that an interpreter may be required. Without cooperation from the patient, particularly with regard to breath-holding instructions, image quality may be significantly degraded.
- Patients must be able to lie flat for ~1 hour and breath hold.
- Patients attending for adenosine stress perfusion imaging should be advised to abstain from caffeine in the 24 hours prior to the study. Those likely to receive dobutamine should be similarly advised to withhold beta-blockers or rate-limiting calcium-channel antagonists.
- Provide details of the patient's renal function, as this will enable appropriate precautions and consent to be taken in renal impairment if gadolinium contrast is to be administered.
- For obese patients, provide details of the patient's weight to assess whether the MRI table and scanner can safely accommodate the patient.
- In patients with suspected metallic foreign bodies in the eyes/orbits (absolute contraindication to MRI), arrange for orbital X-ray imaging to be undertaken before making the request if there is any doubt or the object has not been removed.

Absolute contraindications to CMR

- Pacemaker/implantable cardioverter defibrillator (ICD) or retained/fractured pacing leads.
- Metallic foreign bodies in the eye/orbit.
- Ferromagnetic cerebrovascular aneurysm clips.
- Cochlear implants.
- Insulin pumps.

- There is no documented harm from MRI in pregnancy. Nonetheless, adhering to the precautionary principle, it should be avoided, particularly in the first trimester, unless there is likely to be compelling clinical benefit and the scan cannot be deferred.
- As a precaution, women who are breast-feeding should be advised to express and discard breast milk for 24 hours after receiving gadolinium contrast media.

CMR safety

- Used with the appropriate precautions, CMR is a very safe diagnostic technique. However, the strong magnetic fields employed, typically 1.5 T or 3 T can convert any ferromagnetic object into a projectile with potentially lethal effect. All patients undergoing CMR examination should be screened for ferromagnetic implants, and equipment not specifically deemed *MR safe*, i.e. safe in all MRI environments, should be excluded.
- The radiofrequency pulses used as part of imaging can generate heating effects in wires or implants. Limb-to-limb skin contact can allow current loops to develop with thermal injury at the points of contact. Similar heating and burns can result from such apparently benign objects as standard ECG stickers. These must be removed from the patient prior to the scan, and monitoring carried out with carbon-based MR-safe stickers.
- In addition to the main magnetic field, gradient fields are employed and switched on and off rapidly during imaging to generate various sequences and to allow spatial localization of MR data. These generate very loud noise (>100 dB) and can cause hearing loss. All patients and anyone present in the scanner room should wear protective headphones or earplugs. Rapid gradient switching can also cause unpleasant peripheral nerve stimulation.

Implanted prostheses

- The precautions required depend on the material composition of the device and implant, and where doubt exists, the manufacturer should be consulted. Where no data exist to provide guidance, the risks and benefits of the scan must be carefully weighed. For weakly ferromagnetic devices, a major concern is device/implant dislodgement. Particularly if the scan is not clinically urgent, it is generally recommended that scans are deferred for 6 weeks after implantation to allow the healing process to take place and ensure the device is adequately anchored.
- Coronary and vascular stents are generally only very weakly ferromagnetic. CMR studies can be performed safely in the majority of cases. Similarly, the majority of heart valve prostheses and annuloplasty rings have been labelled as MR safe. Others have been deemed *MR conditional*, i.e. no hazard identified under *specific* imaging conditions. The same applies to closure or occlusion devices, IVC filters, or embolization coils.
- Sternal wires and epicardial pacing leads are safe; however, they can generate artefacts that hamper image interpretation.

Pacemakers/automated ICDs (AICDs)

- These pose potentially significant hazards and there have been reported deaths. In addition to device migration, radiofrequency (RF) heating in leads can result in cardiac injury. The magnetohydrodynamic effects of the strong fields on the ECG can lead to inappropriate device behaviour, and direct effects on device programming/response can occur. New MR-safe pacemakers are now available, but currently

AICDs remain an absolute contraindication to CMR. Retained, particularly fractured device leads pose a significant theoretical safety risk and are regarded as an absolute contraindication to CMR.

- The need for a device should be carefully anticipated and, if indicated, CMR undertaken before implantation if possible, as up to 75% of such patients have or will develop an indication for CMR in their lifetime.
- Implantable loop recorders have been safely scanned and can be deemed MR conditional. They generate considerable artefact and, in theory, their performance can be influenced by strong magnetic fields. They should therefore be interrogated before a scan is undertaken and again afterwards to clear the device buffers of any inappropriate artefactual data that may have accumulated during the scan.

Gadolinium contrast media

- The two principal risks of gadolinium contrast media are anaphylaxis to the gadolinium chelate or one of its excipients and nephrogenic systemic fibrosis (NSF).
- MR contrast media are completely distinct from the iodinated contrast agents used in X-ray-based imaging, so allergy to one does not imply allergy to the other unless it is to a common excipient.
- MR contrast media do not induce renal failure or contrast nephropathy; however, in patients with significant renal impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²), there is a risk of nephrogenic systemic fibrosis—a condition characterized by the development of dermal and multi-organ fibrosis, typically within days to weeks of contrast administration. ~5% of patients experience a fulminant malignant course.
- It has only ever been reported in the context of renal impairment and is thought to be due to the release of free toxic Gd³⁺ ions from their chelate. In this context, cyclic gadolinium chelates appear to be significantly safer than older linear agents.
- It is estimated to occur in 2.4% of patients per study in the context of end-stage renal failure. In patients with an eGFR less than 30 L/min/1.73 m², or in those who are on dialysis, the risks and benefits of contrast administration should therefore be carefully weighed by both patient and physician. If contrast is to be administered, the lowest possible effective dose should be given, and a cyclic gadolinium chelate should be employed. Patients who require renal replacement therapy should undergo haemodialysis immediately after the scan.
- Caution should also be exercised in patients with any degree of renal impairment who are awaiting or who have recently had liver transplants, because of the risk of hepatorenal syndrome.

Unstable patients

- Patients who are haemodynamically or otherwise unstable should not be taken into the scanner. There is limited scope for monitoring, and resuscitation equipment is not MR safe. Any patient requiring cardiopulmonary resuscitation (CPR) has to be transferred out of the scanner first. Together with limited access to the patient, these constraints make CMR an impractical modality for the unstable patient.

Cardiomyopathy assessment

CMR has the unique ability in a single study to non-invasively, accurately, and reproducibly assess LV mass and wall thickness, LV and RV volumes, and myocardial perfusion, as well as the ability to detect myocardial fibrosis and inflammation. It is therefore the modality of choice for the assessment and follow-up of patients with heart muscle disease.

Dilated cardiomyopathy

- Dilated cardiomyopathy is a disorder of heart muscle characterized by LV and/or RV dilation and impairment of systolic function, in the absence of significant coronary artery disease. The ability of CMR to accurately quantify biventricular chamber volumes enables it to detect early LV dysfunction and dilatation, and its reproducibility facilitates serial follow-up and evaluation of response to treatment. CMR with delayed hyperenhancement imaging may also allow the identification of an ischaemic aetiology.
- Patients with a dilated cardiomyopathy and unobstructed coronaries demonstrate either no late gadolinium enhancement (60%) or evidence of mid-wall enhancement correlating with mid-wall fibrosis on histology (30%). A further 10% demonstrate evidence of subendocardial hyperenhancement in a coronary distribution, which may represent previous coronary thromboembolism, spasm, or thrombotic occlusion with spontaneous recanalization.
- Patients with obstructive coronary disease, however, have subendocardial late gadolinium enhancement. CMR may therefore potentially obviate the need for invasive coronary angiography in some patients, and in others disclose the significance of any identified coronary disease, enabling appropriate secondary prevention measures to be instituted.
- The presence of mid-wall late gadolinium enhancement may be of independent prognostic significance and identifies a subgroup of patients at increased risk of all-cause mortality and unplanned hospitalization.
- Imaging in the early phase after gadolinium allows the identification of mural thrombus, which may be encountered in severe LV dysfunction.

Hypertrophic cardiomyopathy

- Hypertrophic cardiomyopathy is an inherited disorder of the cardiac sarcomere characterized by the development of left ventricular hypertrophy in the absence of any extrinsic physiological or pathophysiological stimulus.
- The multiplanar capabilities and high spatial resolution of CMR provide a number of advantages over echocardiography. By avoiding oblique cuts, CMR avoids the overestimation of LV wall thickness that can occur with ECHO. CMR also allows the identification of hypertrophy at the LV apex and the anterolateral free wall, which may be missed on echocardiography. At the level of the basal anteroseptum, a common site for hypertrophy, it allows more accurate differentiation of the LV septum from RV-septomarginal trabeculation, which is often overestimated on echocardiography.

- CMR enables the identification of LVOT obstruction and systolic anterior motion of the mitral valve, and the assessment of associated posteriorly directed MR, although the higher temporal resolution of ECHO provides a distinct advantage in this setting, especially with regard to assessing LVOT obstruction at rest and on exertion.
- CMR can also disclose the presence of accessory papillary muscles and chordae and help determine their role in LVOT obstruction. This can be important to identify prior to consideration of invasive treatment.
- CMR may identify areas of hypocontractility prior to the development of regional hypertrophy.
- It can also readily identify apical trabeculation, enabling apical hypertrophic cardiomyopathy (HCM) to be differentiated from apical LV non-compaction or endomyocardial fibrosis, which may have similar appearances on ECHO.
- Uniquely, CMR can identify late gadolinium enhancement suggestive of fibrosis. This is typically mid-wall in distribution and occurs in areas of hypertrophy. It may also be seen at the LV apex in the apical variant, and in variants with severe mid-ventricular thickening, which can predispose to apical infarction and aneurysm \pm thrombus formation, neither of which can be readily visualized on ECHO. CMR can also accurately assess the extent and distribution of fibrosis induced by alcohol septal ablation, and is therefore of use in evaluating the response to treatment.
- The extent of fibrosis may correlate with a propensity to develop LV-systolic dysfunction and a more malignant natural history.
- CMR with adenosine stress perfusion imaging may identify areas of hypoperfusion that correlate with increased wall thickness.
- CMR can be useful for differentiating sarcomeric HCM from phenocopies, the athlete's heart and cardiac amyloid.
 - Anderson–Fabry's disease is an X-linked recessive disorder resulting from defective or absent lysosomal α -galactosidase-A. This can result in cardiac involvement with concentric LVH but also an asymmetric pattern. Approximately 50% of patients with Anderson–Fabry's disease exhibit mid-wall late gadolinium hyperenhancement, particularly confined to the basal inferolateral wall (>90% of cases with cardiac involvement). The importance of identifying this is highlighted by the fact that 4% of patients with suspected HCM turn out to have Anderson–Fabry's disease and that enzyme-replacement therapy is now available to treat this multisystem condition.
 - Hypertrophic cardiomyopathy remains the most common cause of sudden cardiac death in young people, and, in particular, athletes. The latter often present with a degree of physiological hypertrophy, which can present a diagnostic challenge. However, LV wall thickness is rarely >15 mm, indexed LV volumes in diastole tend to be increased in athletes engaged in dynamic exercise, and there should be no evidence of late gadolinium hyperenhancement. The absence of the latter or the presence of mild hypertrophy (wall thickness 12–15 mm) does not, however, exclude HCM,

and, occasionally, repeat CMR imaging after at least 3 months of deconditioning may be required.

- CMR may also aid differentiation between hypertensive LVH or HCM. Hypertrophy >15 mm is unusual in hypertensive LVH. Levels above 20 mm are strongly suggestive of HCM. In addition, although hypertensive heart disease may be associated with increased LV interstitial fibrosis, the patchy mid-wall late gadolinium enhancement often seen in HCM does not occur.
- CMR in HCM is therefore useful for diagnosis, differential diagnosis, follow-up, planning invasive treatment for LVOT obstruction, and identifying complications. In the future, quantification of the degree of late gadolinium hyperenhancement may also provide prognostic information.

Arrhythmogenic RV cardiomyopathy

- This is an inherited heart muscle disorder that predominantly but not exclusively affects the right ventricle, and that is characterized by fibrofatty replacement of cardiomyocytes.
- CMR is an important modality for diagnostic evaluation, given its ability to precisely and accurately image the right ventricle and, through late gadolinium hyperenhancement imaging, identify areas of fibrosis.
- CMR features and major Arrhythmogenic Right Ventricular Myopathy (ARVC) Task Force criteria include severe RV dilatation and impairment of RV function with little or no LV involvement; localized RV aneurysm formation (akinetic or dyskinetic areas with diastolic bulging); and severe segmental dilatation of the RV.
- Mild global RV impairment or dilatation, mild RV segmental dilatation, and regional RV hypokinesia constitute minor ARVC Task Force criteria, which may be readily identified by CMR.
- ARVC most commonly affects the RV apex, RVOT and subtricuspid region—the so-called triangle of dysplasia.
- $>60\%$ of patients exhibit late gadolinium enhancement of the RV. Approximately 20% of patients may exhibit LV fibrosis.
- LV involvement with wall-motion abnormalities but without significant RV dysfunction is recognized.

LV non-compaction cardiomyopathy

- This cardiomyopathy results from the premature arrest *in utero* of the process of compaction of trabeculated or spongy myocardium in the LV. The normal process of compaction takes place from base to apex, from epicardium to endocardium, and from the septal to the lateral wall.
- The apex is therefore the most frequently involved segment, as this is the last region to compact. Traditionally, diagnosis has relied on echocardiography. However, due to near-field clutter and ECHO drop-out, the apex is poorly visualized with echocardiography. CMR is not subject to these limitations and can provide exquisitely detailed high-spatial-resolution images, facilitating diagnosis.
- The diagnosis is made if the ratio of non-compacted to compacted myocardium is $>2.3:1$ in diastole.

- By examining the LV early after the injection of gadolinium contrast, CMR also allows the detection of LV thrombus, a major complication of LV non-compaction.

Cardiac amyloid

- Primary or AL amyloid clinically involves the heart in over 40% of cases and is a major cause of death in such patients. Secondary or AA amyloid rarely involves the heart. Hereditary amyloidosis, particularly due to amyloidogenic mutations in transthyretin, frequently also involve the heart. In the older age group (>80 years), senile systemic amyloid is a significant problem. CMR can play a significant role in the diagnosis of cardiac involvement.
- There is usually concentric thickening of the LV myocardium due to amyloid infiltration (not hypertrophy as myocyte size is largely unaffected). A significant proportion of patients may experience asymmetric hypertrophy, causing diagnostic confusion with HCM. In the later stages, there is systolic dysfunction with poor myocardial contraction. Commonly seen features such as bi-atrial enlargement and diastolic dysfunction are non-specific. Some patients may exhibit systolic anterior motion of the mitral valve \pm premature closure of the aortic valve as in HCM. Unlike other modalities, CMR with gadolinium contrast can allow tissue characterization with high spatial resolution, and facilitate differential diagnosis.
- CMR can reveal circumferential subendocardial to mid-wall late gadolinium enhancement in up to two-thirds of affected patients. As the septum has endocardium on both sides, this can give rise to a characteristic zebra-stripe pattern of septal late enhancement. The distribution of late enhancement is often in a non-coronary pattern, enabling differentiation from subendocardial myocardial infarction. In addition, the blood pool can appear unusually dark. This is thought to be due to the avid uptake of gadolinium by the infiltrated myocardium, together with more rapid washout from the blood pool. Other CMR features include thickening of the inter-atrial septum, RA free-wall and valve leaflets, together with the consequences of significant diastolic heart failure including pericardial \pm pleural effusions and a dilated IVC.

Sarcoid

- Cardiac involvement can result in life-threatening ventricular arrhythmias, AV-conduction disease, and congestive cardiac failure.
- CMR may reveal patchy mid-myocardial or epicardial late gadolinium enhancement, papillary muscle involvement, or RV subendocardial or free-wall involvement. There may be a subendocardial or transmural pattern of hyperenhancement, which may be confused with myocardial infarction, especially involving the anteroseptal and inferolateral walls. Identification of RV involvement can help guide biopsies. T₂-STIR (short tau inversion recovery) sequences can identify oedema, which may signify acute inflammation and may be useful for identifying active disease. The use of CMR increases the likelihood of diagnosing cardiac involvement over and above clinical criteria, but the diagnosis remains challenging.

Myocarditis

- Acute myocarditis is an important cause of acute heart failure, and in a proportion of patients can progress to a dilated cardiomyopathy or be complicated by sudden cardiac death. Traditionally, diagnosis has relied upon endomyocardial biopsy; however, this often fails to access affected areas of myocardium and therefore suffers from low sensitivity and negative predictive value.
- CMR can identify and quantify regional or global ventricular dysfunction resulting from myocarditis. Changes in LV mass and volumes with resolution of myocardial oedema can be detected by CMR. The inflammatory process can involve the pericardium as part of a myopericarditis in over 50% of patients. CMR can detect the resultant pericardial effusions. T₂-weighted sequences can reveal myocardial oedema. The T₂-STIR sequence further enhances the appearance of oedema by using inversion pulses to suppress the signal from fat and blood.
- Myocardial oedema and inflammation cause expansion of the extracellular space. Gadolinium contrast rapidly diffuses into areas of cellular injury and inflammation, and imaging in the early washout phase can reveal hyperenhancement, denoting capillary leak and hyperaemia. Imaging in the late phase can reveal hyperenhancement. This signifies irreversible myocardial injury with replacement fibrosis and is typically subepicardial to mid-wall in distribution, unlike that due to coronary disease, which is classically subendocardial.
- The identification of hyperenhancement in the early phase, and absence of such enhancement in the late phase denotes inflamed and threatened but potentially reversibly injured myocardium. CMR can be used to guide endomyocardial biopsy and increase diagnostic yield.
- CMR techniques have not been adequately validated with histology, and the CMR criteria for diagnosis (Lake Louise criteria) are based on expert consensus, and, in the context of strong pre-test clinical suspicion, require two of:
 - regional or global increase in signal intensity in T₂-weighted images.
 - increased global myocardial early gadolinium enhancement on T₁-weighted images.
 - the presence of one or more focal lesions on late gadolinium-enhanced T₁-weighted images.
- The above criteria are estimated to have a diagnostic accuracy of ~78%. However, the CMR study should be repeated 1–2 weeks later if there is a strong clinical suspicion for myocarditis but none or only one of the above criteria have been fulfilled. Follow-up scans may also be considered one month or more after diagnosis to assess for resolution and sequelae.

Further reading

Freidrich MG, Sechtem U, Schulz-Menger J, et al (2009). Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol* **53**: 1475–87.

Assessment of cardiac iron status

- There is no physiological means by which excess iron can be removed from the body. Patients with haemoglobinopathies such as β -thalassaemia major and sickle cell disease require repeated transfusions and can therefore develop iron overload.
- Levels of cardiac iron correlate poorly with traditional serum markers of iron status and also with liver iron loading as determined by biopsy. Prior to the introduction of CMR-based assessment of cardiac iron status, iron-overload cardiomyopathy was the leading cause of death in patients with transfusion-dependent anaemias. Although IV and oral chelation therapy exists, prior to the use of CMR there was no accurate way of predicting when to institute therapy and at what intensity.
- Both symptoms of heart failure and a decline in ejection fraction only develop at a very late stage. Many patients with apparently effective chelation as assessed by traditional methods nonetheless succumb to iron-overload cardiomyopathy.
- Lysosomal deposits of microscopic iron particles (haemosiderin) in myocardium cause a shortening of $T2^*$ ($T2$ -star), a relaxation parameter or time constant for the decay in transverse magnetization due to both spin-spin de-phasing and inhomogeneity in the local magnetic field, the latter being heavily influenced by iron. $T2^*$ can be measured in a single breath hold in a highly reproducible way. The normal value for $T2^*$ is 37 ± 5 ms, with values >20 ms generally predicting absence of cardiac iron. Values below 20 ms are associated with progressively increasing iron loading and the development of overt contractile dysfunction.
- A value of <10 ms has a 98% sensitivity and 86% specificity for predicting the development of heart failure within 1 year; 47% of patients with $T2^* < 6$ ms develop heart failure within a year. The same technique can be used to assess liver iron stores and has confirmed that chelation therapy produces a more rapid clearance of hepatic iron stores than cardiac iron.
- This allows the type, and duration of intensity of chelation therapy to be tailored to the patient's risk, and efficacy to be reproducibly and non-invasively monitored, transforming the outlook for these patients.

Further reading

Kirk P, Roughton M, Porter JB, et al (2009). Cardiac $T2^*$ magnetic resonance for prediction of cardiac complications in thalassaemia major. *Circulation* **120**: 1961–8.

Ischaemia and viability assessment

- Myocardial ischaemia can be detected using either gadolinium contrast-enhanced first-pass perfusion imaging with vasodilator stress, or by the evaluation of wall motion under dobutamine stress, analogous to stress echocardiography. Using coronary angiography as a gold standard, first-pass perfusion CMR has a sensitivity of 91% and a specificity of 81% and compares favourably with nuclear SPECT-based techniques. It is not subject to the attenuation artefacts experienced with SPECT and does not involve any ionizing radiation. It also has better spatial resolution and, analogous to PET, may allow quantitative assessment of perfusion, although this is cumbersome and currently only used in research settings.
- Vasodilator stress is achieved by infusing 140 mcg/kg/min of adenosine (3 mg/mL) until there is evidence of a haemodynamic response (typically 3 min), followed by rapid infusion of gadolinium contrast and rapid acquisition of short-axis slices at basal, mid-ventricular and apical level, as contrast enters the myocardium. The sequence requires a very long breath hold, but satisfactory images can be obtained with very gentle breathing at the end of the longest breath hold managed.
- The use of adenosine to achieve vasodilator stress requires abstinence from caffeine-containing food and beverages (e.g. coffee, tea, chocolate, Coca-Cola, Red Bull) ideally for 24 hours prior to testing. It is contraindicated by the presence of high-grade AV-conduction disease or severe asthma. Forty-eight hours' abstinence from beta-blockers or rate-limiting calcium-channel antagonists is essential for dobutamine stress but not for vasodilator stress-based protocols. Adenosine should not be co-administered with dipyridamole, as the latter significantly prolongs the half-life of adenosine and may indeed be used as a stress agent itself.

Practical tip: for stress perfusion imaging, the patient requires two separate IV lines, one large bore (18G or larger), to facilitate rapid contrast bolus infusion and the other for adenosine infusion. BP monitoring should be undertaken using the arm with the contrast line, otherwise BP measurements/cuff inflation may interrupt adenosine infusion.

- A significant limitation of MR-perfusion imaging at 1.5 T is the presence of dark-rim artefact, which may lower the specificity for detecting subendocardial perfusion defects. Imaging at higher field strengths (3 T) affords higher contrast-to-noise ratio and also reduces the risk of this artefact, further improving diagnostic specificity.
- Artefacts can often be identified by examining rest perfusion images, and interpretation can be further enhanced by examining images acquired in the late phase following gadolinium enhancement. The latter technique detects fibrosis and can further facilitate the differentiation of ischaemia from infarction.
- The limited space inside the scanner bore and the lack of MR-safe resuscitation equipment represent relative disadvantages of MR. Also, the magnetohydrodynamic effects distort the ECG and make the use of

ST-segment monitoring impossible. However, ST-change is a late stage in the ischaemic cascade, and rhythm monitoring, direct observation, and communication with the patient readily obviate the need for this.

- Despite these limitations, normal MR perfusion imaging affords >99% event-free survival at 3 years.

Assessment of viability and hibernating myocardium

- Over 60% of patients with heart failure have ischaemic heart disease as the predominant cause.
- Viable myocardium can be defined as myocardium supplied by coronary arteries with flow-limiting coronary disease that exhibits contractile dysfunction in the absence of significant scar tissue and therefore has *potential* for contractile recovery following successful revascularization. Hibernation is defined retrospectively by the presence of evidence of functional recovery of hypocontractile myocardium following revascularization.
- Successful revascularization of patients with significant (>4 segments) ischaemic but viable myocardium appears to improve ejection fraction and prognosis proportionate to the degree of LV impairment, according to meta-analysis of outcome data from numerous retrospective studies and registry data (prospective studies to assess this are under way and due to report shortly). However, revascularization of patients without viable myocardium offers no apparent prognostic benefit and may indeed cause harm, because of the higher risks involved in the setting of significant LV impairment.
- Late gadolinium enhancement CMR imaging allows the identification of myocardial fibrosis which, when due to ischaemia, extends from the subendocardium towards the epicardium. The technique, by virtue of its greater spatial resolution, is superior to both PET and SPECT at identifying fibrosis. Viability is proportional to the transmural extent of fibrosis, with segments showing >50% fibrosis being defined as non-viable. Specificity can be improved by combining the technique with low-dose dobutamine stress CMR evaluation of wall-motion abnormalities. This is particularly helpful in patients with intermediate transmural extent of infarction and may yield a sensitivity of ~95% and specificity of ~85% when combined with late-enhancement imaging.
- CMR has shown that, in the absence of fibrosis, significant functional recovery can take place even in thinned (<5 mm) and remodelled myocardium that would traditionally have been regarded as non-viable. Furthermore, the presence of late enhancement appears to be a powerful independent predictor of mortality.

CMR in valvular heart disease

- Doppler echocardiography remains the modality of choice for the evaluation of valvular heart disease in the majority of circumstances, because of its higher temporal resolution. CMR provides an alternative, however, where ECHO windows are challenging or when there are contraindications to TOE or a marked discrepancy between ECHO data and the clinical picture.
- CMR is also useful where additional anatomical information is required, such as the dimensions of the aorta in a patient with bicuspid aortic valve disease or suspected coarctation of the aorta, or where revascularization and valve repair are being planned and information about myocardial viability is needed. It is particularly useful for following up aortic regurgitation secondary to aortic root disease where serial, accurate, and reproducible measurements of root dimensions are needed.
- Phase-contrast flow velocity mapping can enable determination of peak flow velocities, estimation of valve gradients, and relatively accurate quantification of regurgitant fractions. Through-plane flow maps are used to characterize flow jets and facilitate accurate positioning for in-plane measurements of flow velocity. Measurements can be taken in a single breath hold.
- The ability of CMR to accurately and directly quantify ventricular volumes allows the separate estimation of stroke volume and the calculation of interventricular stroke volume difference, which is particularly useful for MR, where the combination of annular through-plane motion and the altering geometry of the valve plane itself make the accurate use of phase-contrast flow velocity mapping difficult.
- CMR can be used to planimeter the aortic valve, allowing direct estimation of aortic valve area. In addition, root dimensions and aortic, iliac, and femoral arterial anatomy can be assessed, providing useful information where percutaneous aortic valve replacement is being considered.
- The multiplanar capability of CMR allows a stack of images to be taken through the mitral valve to disclose the mechanism of MR and assess the suitability of leaflets for repair.
- CMR allows the pulmonary valve and right ventricle to be imaged in exquisite detail and is invaluable for the precise evaluation of pulmonary regurgitation as well as pulmonary artery anatomy in patients with tetralogy of Fallot and other congenital heart diseases with significant right ventricular involvement. It also allows ready estimation of shunt fractions, and thereby facilitates the evaluation of both intra- and extra-cardiac shunts.

CMR for congenital heart disease

- The lack of ionizing radiation (a particular concern where serial evaluation is required in adolescents or young adults), a wide field of view, and the versatile multiplanar 2D and 3D imaging capability afforded by CMR make it the modality of choice for the evaluation and follow-up of patients with congenital heart disease. This is particularly true in those with complex anatomy, e.g. Fontan circulation, or after repeated surgical repairs where scar tissue can give rise to poor ECHO windows.
- The wide field of view allows viscerotrial *situs* and cardiac position to be readily assessed. Atrioventricular and ventriculoarterial concordance can also be evaluated.
- Accurate assessment of pulmonary and aortic flows allows shunt ratios (Q_p/Q_s) to be readily calculated. Detailed visualization and flow mapping of the atrium and interatrial septum can enable assessment of ASD for percutaneous or surgical closure, and ready identification of anomalous pulmonary venous drainage. Assessment of the effects of lesions on RV volumes and function may be critical for determining the nature and timing of any surgical intervention.
- The origin and proximal course of coronary arteries can be delineated with whole-heart coronary imaging sequences, allowing identification of anomalous coronary arteries and definition of their course with respect to the aorta and pulmonary arteries. This can facilitate identification of malignant courses and planning for surgical repair. CMR can also be used to assess the integrity of the proximal coronaries after Bentall repair for aortic root disease, the Ross procedure, and the arterial switch operation for transposition of the great arteries (TGA). This can also be combined with MR perfusion imaging to assess functional consequences.
- CMR is particularly adept at imaging the aorta and other great vessels. Patent ductus arteriosus (PDA) and associated anomalies are readily defined. Aortic coarctation can be comprehensively assessed, including lesion severity and suitability for percutaneous treatment, or evaluation of re-coarctation or aneurysm formation following surgical repair.
- The unrivalled clarity with which CMR images the RV, together with the functional information it provides, makes it the ideal means for following up pulmonary regurgitation and RV function in repaired tetralogy of Fallot.
- In recent years, the detection of right ventricular late gadolinium enhancement, signifying fibrosis, has emerged as potentially prognostically important in patients with systemic right ventricles, e.g. transposition of great vessels treated by atrial redirection surgery. CMR can therefore provide comprehensive evaluation of anatomy, ventricular function, valve function, perfusion, and tissue characteristics in one non-invasive study.

CMR for pericardial disease

The ability of CMR to image in any plane with high spatial resolution, and its tissue-characterizing ability, makes it the modality of choice for the assessment of pericardial disease. CMR can allow a detailed assessment of the pericardial anatomy, detect the presence of active inflammation, identify and often characterize pericardial tumours and cysts, and help define the haemodynamic consequences of pericardial disease.

Pericarditis and pericardial effusions

- In acute pericarditis, CMR with T₂-STIR sequences can often uniquely delineate areas of high signal in the pericardium, reflecting acute inflammation. CMR can also reveal pericardial thickening, and the use of appropriate pre-pulses can facilitate the delineation of pericardium from surrounding fat or fluid.
- CMR is a particularly sensitive technique for the assessment of pericardial effusions. This can be readily accomplished with echocardiography; however, CMR can be helpful in the setting of loculated pericardial effusions; detecting pericardial haematoma; in those with poor ECHO windows; and in patients where neoplasia is suspected and information is required about surrounding tissues.
- CMR can be used to assess the sequelae of acute pericarditis. The administration of gadolinium can help to identify myocardial involvement, i.e. myopericarditis, and, in the late phase, CMR can be used to diagnose constrictive pericarditis and to assess for surgery.

Constrictive pericarditis

- The pericardium is thickened and often low signal due to the presence of fibrotic tissue and calcium, which has poor water content. A pericardial thickness >4 mm should raise the index of suspicion for constriction. However, normal pericardial thickness, i.e. 2 mm or less, does not exclude the condition. Other features that may be present include bi-atrial dilatation, engorgement of the IVC and hepatic veins, pleural effusions, narrowing of the RV cavity, and reduction in the size of the AV groove. RV long-axis function, however, is often preserved in distinction to the situation with a restrictive cardiomyopathy. CMR tagging techniques can be used to identify fibrous continuity between visceral and parietal pericardium.
- Real-time free-breathing cine sequences can be used to detect the haemodynamic effects of pericardial constriction. The RV normally starts to fill earlier than the LV. The constricting pericardium prevents expansion of the RV that would normally accommodate this filling. As a result, the interventricular septum is pushed from right to left in early diastole ('early septal bounce'). Inspiration, by increasing RV filling, exacerbates the situation increasing left-ward septal movement in early diastole, particularly after the first heart beat following inspiration. These changes are not seen in restrictive cardiomyopathy.

Pericardial defects

- There may be partial or complete absence of the pericardium. Most commonly, the left side of the pericardium is involved. There is usually marked displacement of the heart, and interposition of a tongue of lung parenchyma between the aorta and pulmonary artery and between the inferior surface of the heart and the diaphragm.
- CMR can also be used to identify associated conditions such as a PDA, tetralogy of Fallot, ASD, and congenital mitral stenosis. Partial pericardial defects may be complicated by cardiac herniation, particularly of the left atrial appendage. The latter can become strangulated and undergo infarction.

Pericardial cysts

- These are congenital, usually unilocular, cystic structures arising from the pericardium. They appear high signal on T₂-weighted images because of their water content and do not enhance with gadolinium as they have no direct blood supply. CMR therefore allows them to be readily differentiated from other potential cystic structures or neoplasms.

CMR evaluation of cardiac masses

- The wide field of view offered by CMR, and its ability to image in any plane and to non-invasively characterize tissue makes CMR the modality of choice for evaluating cardiac masses.
- Intracardiac thrombus is readily identified by imaging in the early washout phase following gadolinium administration. Thrombus is avascular, does not take up contrast, and appears dark. Imaging in the late phase can identify areas of late myocardial gadolinium uptake, revealing sites of infarction, which can constitute the substrate for mural thrombosis and further highlight low-signal thrombus.
- Primary cardiac tumours are rare. The majority that occur (>75%) are benign. The commonest benign lesion by far is the myxoma (50% of lesions). Lipomas, papillary fibroelastomas, and, in the paediatric population, rhabdomyomas, and fibromas are comparatively rarer.
- The most common primary malignant tumours are sarcomas, followed by primary lymphomas. Angiosarcomas are the most common form of cardiac sarcoma and predominantly involve the right atrium (~75%).
- Metastatic lesions are over 20 times more common than primary tumours. The heart may be involved via haematogenous spread (e.g. melanoma, lymphoma), lymphogenous spread (e.g. lymphoma), direct extension (e.g. breast, lung), or via the venous system (e.g. renal cell carcinoma).
- CMR allows the location of lesions to be assessed (i.e. intramural versus intracavity) and identification of multiple (metastatic) deposits. It can also identify pleural and pericardial effusions, which can raise the index of suspicion for malignant disease.
- The CMR evaluation of any suspected cardiac mass involves T₁- and T₂-weighted spin ECHO sequences; dynamic evaluation with gradient-ECHO-based cines; assessing the presence of contrast enhancement; and perfusion imaging with gadolinium; as well as late-enhancement imaging. The technique of tagging—marking structures with intersecting tags to form a grid—can be used to assess the deformation of masses with cardiac contraction, and thereby reveal their continuity or relationship with cardiac muscle.
- CMR can also facilitate imaging of vascular structures and surrounding anatomy as part of planning a surgical approach.
- Differential diagnosis is approached by considering the location, appearance, and signal characteristics of tumours, and integrating these with the wider clinical picture.

Drugs for the heart

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Antiplatelet agents

Antiplatelet agents are used to reduce the risk of arterial thrombus formation by preventing platelet activation and aggregation. Antiplatelet agents have a role in the primary and secondary prevention of cardiovascular (CV) disease.

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Antiplatelet agents: aspirin

Mode of action

Aspirin blocks the thromboxane A₂ pathway of platelet activation by irreversibly acetylating cyclo-oxygenase. The effect of aspirin persists for the lifespan of the platelet.

Clinical evidence

Secondary prevention: Data to support the use of aspirin in secondary prevention of CV disease have been accruing since the 1980s, following the publication of the landmark Second International Study of Infarct Survival (ISIS-2), where the use of aspirin 300 mg in acute myocardial infarction (AMI) reduced mortality by 23%. The Antithrombotic Trialists' Collaboration, concludes that post AMI, aspirin reduces the risk of further CV events by 25% (number needed to treat (NNT) = 28 over 2 years).

Primary prevention: The role of aspirin in primary prevention is less clear, as the cardiovascular benefits must be balanced against the risk of adverse events, in particular, the risk of gastrointestinal (GI) bleeds. Aspirin should not be prescribed for primary prevention in low- or moderate-risk patients (i.e. those with a calculated CV risk less than 20% over 10 years).

For patients at high CV risk (>20% over 10 years), the decision to initiate aspirin is controversial, with most clinicians avoiding use even in this high-risk group. While low-dose aspirin will prevent approximately 10–15 vascular events for every 1000 patients treated for 2 years, it increases the risk of bleeding two to threefold. In hypertensive patients, there is an increased risk of intracranial haemorrhage during treatment with low-dose aspirin; therefore, blood pressure should be controlled to less than 150/90 mmHg if it is initiated for primary prevention.

Place in therapy

The benefit of aspirin in secondary prevention is evident for all presentations of CV disease, including myocardial infarction (MI), acute coronary syndromes, unstable angina, chronic stable angina, post-CABG (coronary artery bypass graft), ischaemic stroke, and peripheral vascular disease. Aspirin is no longer recommended for routine use for primary prevention, as the benefit to risk ratio is finely balanced.

Platelet aggregation

Platelet aggregation occurs as a result of the formation of fibrinogen bonds between glycoprotein IIb/IIIa receptors expressed on the surface of activated platelets. Platelets are activated by a number of pathways, with specific inhibitors (see Table. 2.1).

Table 2.1 Platelet activation pathways and drug inhibitors

Pathway	Drug inhibitors
Thromboxane A ₂	Aspirin
ADP mediated	Clopidogrel Prasugrel Ticlopidine Ticagrelor
Thrombin	Heparin (weak) Bivalirudin
Glycoprotein IIb/IIIa receptors	Abciximab Eptifibatide Tirofiban

ADP = adenosine diphosphate.

Indications for aspirin

- *Secondary prevention of CVD:*
 - cardiac—angina, post PCI (percutaneous coronary intervention) or CABG, post MI
 - stroke—*ischaemic*
 - peripheral arterial disease (PAD)
- *Primary prevention of CVD:* generally no longer routinely recommended
- Atrial fibrillation (AF): doses of 75–300 mg may be used in those at moderate to high risk of thrombotic events, especially where warfarin is unsuitable or not tolerated.

Adverse effects of aspirin

- Aspirin, even at low doses, can precipitate bronchospasm in up to 20% of asthmatic adults.
- Gastric side-effects are common and range from a feeling of nausea in the hour or so after the dose to major GI bleeds. Aspirin is associated with a greater risk of bleeding from duodenal ulcers than gastric ulcers and occurs more commonly in the early days of treatment.
- Risk factors for bleeding, which should be assessed, include previous GI events, older age, and use of anticoagulants, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs). Prophylaxis with a proton pump inhibitor (PPI) should be considered in patients with multiple risk factors.

Resistance

- The effectiveness of aspirin in clinical practice is affected by 'aspirin resistance'. This occurs relatively commonly in up to 10% of patients treated. However, as the testing of platelet activity is not widely undertaken, this is rarely identified.

Contraindications and cautions

- **Contraindications:** known allergy, active peptic ulceration, history of recent GI bleeding, history of recent intracranial bleeding, and bleeding disorders including haemophilia, von Willebrand's disease, thrombocytopenia and severe liver disease.
- **Cautions:** asthma, uncontrolled hypertension, previous peptic ulceration (risk of GI bleeding; PPIs or H₂-receptor antagonists may be considered for prophylaxis).

Risk factors for GI bleeds with aspirin

- Age: risk doubles with each decade of life above 55 years.
- Men: risk is twice as high in men as in women.
- History of GI ulcer, bleed, or perforation.
- Concomitant medications, such as NSAIDs, anticoagulants, selective serotonin reuptake inhibitors (SSRIs).
- Serious co-morbidities, such as CV disease, liver or kidney disease, diabetes.
- Need for prolonged NSAID use—osteoarthritis, rheumatoid arthritis, chronic low back pain.
- Presence of *H. pylori*.
- Excess alcohol.
- Heavy smoking.

Strategies to reduce GI bleeding risk with aspirin

- Prescribe 75 mg daily, unless a higher dose is indicated.
- Advise the patient to take the dose with or after food.
 - Do not use enteric coated preparations, these do not reduce the risk of GI events.
- Review concurrent medications and stop or reduce the dose of any that might increase the risk of bleeds.
- Advise sensible drinking.
- Advise smokers to quit or reduce their smoking.
- Consider co-prescribing a PPI for those with multiple risk factors.

Drug interactions with aspirin

- **Analgesics:** avoid concomitant use with NSAIDs as this increases the risk of adverse effects.
- **Anticoagulants:** increased risk of bleeding with warfarin and other anticoagulants. Avoid concomitant use unless there is a compelling indication for both.
- **Antidepressants:** increased risk of bleeding with SSRIs and venlafaxine.
- **Cytotoxics:** aspirin reduces the excretion of methotrexate; avoid concomitant use where possible, or ensure close monitoring of methotrexate dose.

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Antiplatelet agents: thienopyridines

Mode of action

Thienopyridines irreversibly block the binding of ADP to platelet receptors, and hence prevent expression of the active glycoprotein IIb/IIIa receptor. The first agent in this class, ticlopidine, has been superseded in clinical practice by the use of clopidogrel which has fewer serious adverse effects. Prasugrel was launched in 2009, and 2010 saw the introduction of ticagrelor.

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Antiplatelet agents: clopidogrel

Clinical trial data

In the CAPRIE (Clopidogrel versus Aspirin in Patients at risk of Ischemic Events) study (1997), clopidogrel demonstrated a small advantage over aspirin in terms of protecting patients from recurrent CV events. As the clinical advantage over aspirin for this indication is small and the relative cost is large, clopidogrel should only be employed for monotherapy in patients who are unable to tolerate aspirin first line. There is no evidence to support the use of clopidogrel for primary prevention of CV disease.

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study (2000) compared aspirin monotherapy to clopidogrel and aspirin dual therapy in patients for up to 9 months post-NSTEMI (non-ST-segment elevation MI) and demonstrated a 2% reduction in major CV events with dual antiplatelet therapy. The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study (2005) demonstrated that aspirin/clopidogrel dual therapy reduced death and CV events at four weeks following the acute event compared to aspirin alone.

Place in therapy

Clopidogrel monotherapy is licensed for the secondary prevention of cardiovascular events in patients post MI or stroke, or with peripheral vascular disease. Clopidogrel is also licensed for use in combination with aspirin for patients following acute coronary syndromes (ST-segment elevation MI (STEMI) and NSTEMI). Clopidogrel should not be used for the primary prevention of CV events. Clopidogrel may also be used for prevention of CV events following procedures such as intracoronary stent implantation (bare metal or drug-eluting) or patent foramen ovale (PFO) closure, or following transapical valve implantation.

Dosing

Clopidogrel is prescribed at a maintenance dose of 75 mg daily for most indications. In STEMI and NSTEMI, a loading dose of clopidogrel 300–600 mg should be given as early as possible following presentation, and 75 mg daily continued for up to one year; aspirin should be continued indefinitely. Recent data from CURRENT-OASIS7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention) indicate that a higher clopidogrel dose of 150 mg daily may be useful in the first week of treatment following a STEMI especially post-PCI.

The dual-therapy aspirin/clopidogrel regimen is also used for up to one year following PCI, particularly where intracoronary stents have been deployed to reduce the risk of stent thrombosis.

Indications and dosing for clopidogrel

See Table 2.2.

Table 2.2 Indications and dosing for clopidogrel

Indications	Dosing
Secondary prevention of CV events in patients post-MI or stroke, or in patients with PAD	Clopidogrel monotherapy; 75 mg daily Usually only in patients unable tolerate aspirin first line
STEMI	Use in combination with aspirin—300–600 mg at presentation then 75 mg daily. Continue for at least 4 weeks post-event (NICE)
NSTEMI	Use in combination with aspirin—300–600 mg at presentation then 75 mg daily. Continue for at least one year post-event
Post-PCI with stent insertion	Use in combination with aspirin—300–600 mg as early as possible prior to procedure, then 75 mg daily. Continue for at least: <ul style="list-style-type: none"> ● 4 weeks post bare metal stent insertion ● 1 year post drug-eluting stent insertion

NICE = National Institute for Health and Clinical Excellence.

Contraindications and cautions

- *Contraindications:* hypersensitivity to clopidogrel, severe hepatic impairment, active pathological bleeding
- *Cautions:* patients at increased risk of bleeding, recent cerebrovascular accident (CVA), renal impairment

Usual initiation and maintenance dose

The usual dose is 300–600 mg loading in the acute setting or pre-procedure, followed by 75 mg daily thereafter.

Early cessation of clopidogrel therapy post-stent insertion is the largest single risk factor for stent thrombosis, which is associated with significant mortality. Patients must be encouraged to persist with therapy, and alternative agents initiated if they are unable to tolerate clopidogrel due to adverse events.

Risk factors for stent thrombosis

See Table 2.3.

Table 2.3 Risk factors for stent thrombosis

Risk factor	Hazard ratio	P
Premature cessation of antiplatelet therapy	89.78	<0.001
Renal failure	6.49	<0.001
Bifurcation lesion	6.43	<0.001
Diabetes	3.71	<0.001
Reduction in LV function by 10%	1.09	<0.001

Iakovou I, Schmidt T, Bonizzi E, et al. (2005). Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* **293**: 2126–30.

Adverse effects

- The single most troubling adverse effect of clopidogrel is skin rash. Care should be taken to distinguish self-limiting X-ray contrast-media-induced skin rash, which occurs early (within one week of PCI), to avoid unnecessary cessation of clopidogrel. Minor rashes may be managed by use of antihistamines, but often alternative therapies such as prasugrel or ticlopidine will be required.
- GI side-effects are reported relatively commonly, and include diarrhoea, abdominal pain, and dyspepsia.
- Bleeding and bruising are common, particularly where aspirin and clopidogrel are used in combination. There is a small risk of haematological disorders including thrombocytopenia and neutropenia.

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Antiplatelet agents: prasugrel

Mode of action

The pharmacological benefits of prasugrel over clopidogrel are an earlier onset of anti-aggregatory effects (significant antiplatelet effects are seen within half an hour of loading) and less inter-patient variability in terms of antiplatelet response.

Clinical evidence

The TRITON TIMI 38 (Trial to Access Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel –Thrombolysis in Myocardial Infarction) study compared prasugrel to clopidogrel (on a background of aspirin therapy) in patients with acute coronary syndrome (ACS) undergoing immediate or delayed PCI, and demonstrated significantly fewer major CV events in the prasugrel-treated group but at the expense of an increased risk of bleeding.

Place in therapy

Prasugrel, used in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with ACS (STEMI, NSTEMI, or unstable angina) undergoing primary or delayed PCI. Patients with a history of stroke or transient ischaemic attack (TIA) did worse on prasugrel than on clopidogrel, and as a result this is a contraindication to therapy. Low body weight and age above 75 years was also associated with no net clinical benefit and therefore the agent should be used cautiously in this group—a lower maintenance dose may be employed. Prasugrel is more effective than clopidogrel in patients with diabetes.

Dosing

Prasugrel 60 mg loading dose followed by 10 mg daily thereafter (maintenance dose should be reduced to 5 mg daily if used in patients over the age of 75 years or those of low body weight, <60 kg). Prasugrel should be continued for a period of one year after the acute event.

Drug interactions with prasugrel

- **Anticoagulants:** concomitant use of clopidogrel with warfarin is not routinely recommended due to the increased risk of bleeding; however, in clinical practice the use of aspirin, clopidogrel, and warfarin is not uncommon, where patients have compelling indications for all three. This should be undertaken with extreme caution and close supervision.
- **Ulcer-healing drugs:** the antiplatelet effect of clopidogrel may be reduced by concomitant use of PPIs. Many centres are recommending a H₂ antagonist, such as ranitidine, first line in patients requiring an acid suppressant, except where the benefits of PPIs are considered to outweigh the potential risks, for example, patients undergoing active ulcer healing.

NICE indications for prasugrel (October 2009)

Prasugrel should be considered as an option in patients undergoing only when:

- immediate primary PCI for STEMI is planned, or
- stent thrombosis has occurred during clopidogrel therapy, or
- the patient has diabetes mellitus.

Contraindications and cautions

- *Contraindications:* hypersensitivity, history of CVA or TIA, active bleeding disorder, severe hepatic impairment
- *Cautions:* those at increased risk of bleeding—over 75 years and body weight <60 kg, renal impairment and moderate hepatic impairment, Asian patients (due to limited clinical experience), pregnancy, and lactation.

Usual initiation and maintenance dose

60 mg loading dose followed by 10 mg daily thereafter. Maintenance dose may be reduced to 5 mg in patients at high risk of bleeding.

Adverse effects of prasugrel

- Bleeding occurs commonly and is particularly problematic in the elderly (>75 years) or patients of low body weight (<60 kg)—a lower maintenance dose may be considered in these groups.
- Anaemia, epistaxis, GI haemorrhage, haematuria are all commonly reported.
- Rashes.

Drug interactions with prasugrel

No significant drug interactions have been identified.

Intravenous antiplatelet agents

Glycoprotein IIb/IIIa (GPIIb/IIIa) receptor inhibitors

Abciximab, a monoclonal antibody, is indicated for the prevention of ischaemic cardiac complications in patients undergoing PCI and for patients presenting with unstable angina who are scheduled to undergo PCI.

Small-molecule GPIIb/IIIa receptor inhibitors, eptifibatid or tirofiban are indicated for the prevention of early MI in patients presenting with STEMI or unstable angina.

Recommendations for use of GPIIb/IIIa inhibitors

Adapted from the European Society of Cardiology (ESC) guidelines for the management of NSTEMI-ACS.

- In patients with ACS at intermediate or high risk, particularly patients with elevated troponins, ST depression, or diabetes, either eptifibatid or tirofiban is recommended, in addition to oral antiplatelet agents, for initial early treatment.
- Patients who received initial treatment with eptifibatid or tirofiban prior to angiography, should be maintained on the same drug during and after PCI.
- In high-risk patients not pre-treated with GPIIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography.
- GPIIb/IIIa inhibitors must be combined with an anticoagulant.
- Bivalirudin may be used as an alternative to GPIIb/IIIa inhibitors plus unfractionated heparin/low molecular weight heparin (UFH/LMWH).
- When coronary anatomy is known and PCI planned to be performed within 24 hours with use of GPIIb/IIIa inhibitors, the most secure evidence is for abciximab.

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Angiotensin-converting enzyme inhibitors

(e.g. captopril, enalapril, lisinopril, ramipril, perindopril)

Mode of action

Angiotensin-converting enzyme inhibitors (ACE-Is) block the conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, which increases sodium and water retention. ACE-Is therefore lead to vasodilatation and prevent the build up of fluid that would result from aldosterone release.

Clinical trial data

ACE-Is are supported by a wealth of clinical trials data across a range of indications including:

- *Hypertension*: numerous clinical studies confirm the blood pressure lowering efficacy of ACE-I.
- *Heart failure* (SAVE (Survival and Ventricular Enlargement) 1993, enalapril; SOLVD (Studies of Left ventricular Dysfunction) 1994, enalapril; ATLAS (Assessment of Treatment with Lisinopril and Survival) 1999, lisinopril). Meta-analyses concludes that ACE-Is reduce mortality in heart failure (HF) by approximately 25%, with a substantial reduction in the risk of hospitalization.
- *Post-MI secondary prevention* (AIRE (Acute Infarction Ramipril Efficacy) 1994, ramipril; GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico) 1994, lisinopril; ISIS-4 1994, captopril). ACE-Is initiated within 24 hours of presentation reduce the risk of death by approximately 7% compared to placebo in the first four to six weeks post-MI. In the longer term, mortality is reduced by ~13% in unselected patients, with greater benefits in those with post-MI heart failure. Long-term follow-up of the SOLVD study showed a significant reduction in all-cause mortality associated with ACE-I treatment, even at 12 years post index event.
- *CV risk reduction* (HOPE (Heart Outcomes Prevention Evaluation) 1999, ramipril; EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) 2004, perindopril). ACE-Is have been shown to reduce the risk of CV events in patients who are at high risk of events, such as those with established atherosclerotic disease.

Choice of agent

Not all ACE-Is are licensed for use in all different cardiovascular indications. It is recommended that a licensed agent, with trial evidence to support its use, is chosen for the indication being managed.

Dose

- *For essential hypertension*, the dose should be titrated until blood pressure control is achieved, bearing in mind that higher ACE-I doses confer better CV protection.

- For other indications, particularly heart failure and for cardioprotection in those with or at risk of cardiovascular disease, the ACE-I MUST be titrated to the target dose or the maximal tolerated dose if the target dose cannot be achieved (i.e. due to hypotension, renal dysfunction, etc.).

Compelling indications for ACE-I use

- *Hypertension*: all non-black patients <55years old
- *Heart failure*: all patients with any degree of left ventricular systolic function, initiated as soon as possible following diagnosis
- *Post-MI secondary prevention*: all patients following an MI, initiated during the inpatient phase of treatment
- *CV risk reduction*: all patients with symptomatic or asymptomatic CVD.

Contraindications and cautions

- *Contraindications*:
 - aortic/mitral stenosis
 - angioedema (any cause)
 - hypersensitivity to ACE-Is
 - bilateral renal artery stenosis
 - pregnancy.
- *Cautions*:
 - hypotension (systolic blood pressure <90 mmHg)
 - Patients on high-dose diuretics (i.e. furosemide >80 mg daily)
 - Breast-feeding
 - Moderate to severe renal impairment (i.e. creatinine >150 $\mu\text{mol/L}$ or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²)—seek specialist advice for initiation.

Initiation and target doses of commonly used ACE-Is

See Table 2.4.

Table 2.4 Indications and doses for commonly used ACE-Is

Agent	Starting dose	Target dose
Enalapril	2.5–5 mg daily	40 mg daily (dose may be divided)
Lisinopril	2.5–10 mg daily depending on indication	35–80 mg daily
Perindopril	2–4 mg once daily	4–8 mg daily depending on indication
Ramipril	1.25–2.5 mg daily	10 mg daily (dose may be divided)

Monitoring

- Obtain baseline BP and urea and electrolytes (U&Es) before initiation
- Check BP and U&Es within two weeks of initiation or change of dose, then annually
- If serum creatinine increases by more than 20% (or eGFR falls by more than 15%) after initiation, stop ACE-I and seek specialist advice.
- ACE-I dose should only be increased if:
 - systolic blood pressure >90 mmHg
 - serum creatinine increases by less than 20% (or eGFR falls by less than 15%) on each dose titration
 - potassium <5.5 mmol/L.
- *Hyperkalaemia*: advise low-potassium diet, ensure adequate fluid intake. Reduce dose if $K^+ >5.5$ mmol/L; withdraw ACE-I if $K^+ >6$ mmol/L.

Dealing with adverse effects

- *First-dose hypotension*: use a long-acting agent, avoid excessive diuresis prior to initiation. First dose may be given at night before bed to reduce the risk of hypotension and associated falls.
- *Dry cough*: may dissipate over time if patient persists with therapy. If troublesome, withdraw agent and re-introduce the same or an alternative ACE-I. Consider an angiotensin receptor blocker (ARB) if cough recurs/persists.
- *Angioedema*: a rare but potentially life-threatening adverse effect. ACE-I therapy should be stopped and specialist advice sought before re-initiation.
- *Rash*: switch ACE-I and if rash persists consider ARB.

Key drug interactions with ACE-Is

- *Ciclosporin*: increases risk of hyperkalaemia
- *Diuretics*: enhances hypotensive effect
- *Lithium*: increases lithium levels
- *Potassium supplements*: increased risk of severe hyperkalaemia.

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Angiotensin receptor blockers (ARBs, also referred to as angiotensin II receptor antagonists, AIIRAs)

(candesartan, irbesartan, losartan, telmisartan, valsartan)

Mode of action

Angiotensin receptor blockers (ARBs) bind to the angiotensin II receptors and therefore block the action of angiotensin II. Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, which increases sodium and water retention. ACE-Is therefore lead to vasodilatation and prevent the build up of fluid that would result from aldosterone release. Unlike ACE-Is the ARBs do not inhibit the breakdown of bradykinin that is responsible for ACE-I-induced cough.

Clinical trial data

ARBs are supported by fewer clinical trials than ACE-Is, but do have data across a range of indications including:

- *Hypertension*: numerous clinical studies confirm the blood-pressure-lowering efficacy of ARBs.
- *Heart failure*: conflicting data emerged from early studies, but CHARM (Candesartan in Heart Failure—Assessment of Mortality and Morbidity) confirmed that candesartan reduced the risk of CV mortality or CV hospitalization in patients with HF, alone or in addition to ACE-I therapy, and with or without concurrent β -blocker therapy. (ELITE-II (Evaluation of Losartan in the Elderly, 2000, losartan; ValHeFT (Valsartan Heart Failure Trial), 2001, valsartan; CHARM, 2006, candesartan)
- *Post-MI heart failure*: valsartan 160 mg bd was non-inferior to captopril in protecting against death and CV event in patients with post MI heart failure (VALIANT (Valsartan in Acute Myocardial Infarction Trial), 2003)*
- *CV risk reduction*—telmisartan 80 mg daily was non-inferior to ramipril 10 mg daily in protecting against CV events in patients with CV disease (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril, 2008)*.

Choice of agent

Not all ARBs are licensed for use in all the cardiovascular indications. It is recommended that a licensed agent, with trial evidence to support its use, is chosen for the indication being managed.

* **Note**: in these and other studies where ACE-Is and ARBs have been combined in one of the treatment arms, there has been an increase in adverse events (renal dysfunction, symptomatic hypotension, hyperkalaemia), with no demonstrable improvement in outcomes, with the exception of the CHARM study. Therefore, the use of an ACE-I and ARB in combination should generally be avoided.

Dose

- For essential hypertension, the dose should be titrated until BP control is achieved
- For other indications, particularly heart failure and for cardioprotection in those with or at risk of cardiovascular disease, the ARB MUST be titrated to the target dose or the maximal tolerated dose if the target dose cannot be achieved (i.e. due to hypotension, renal dysfunction etc.).

Compelling indications for ARB use

- *Hypertension*: second line to ACE-I (i.e. ACE-I-intolerant patients) for non-black patients aged <55 years
- *Heart failure*: second line to ACE-I (i.e. ACE-I-intolerant patients) in all patients with any degree of left ventricular systolic function, initiated as early as possible following diagnosis
- Candesartan may also be considered in addition to ACE-I for inpatients remaining symptomatic despite optimal ACE treatment, if they are unable to tolerate spironolactone
- *Post-MI heart failure*: second line to ACE-I (i.e. ACE-I-intolerant patients); valsartan may be considered for patients with post-MI heart failure
- *CV risk reduction*: second line to ACE-I (i.e. ACE-I-intolerant patients); telmisartan may be considered in all patients with symptomatic or asymptomatic CVD.

Contraindications and cautions

- *Contraindications*:
 - hypersensitivity to ARBs
 - pregnancy
 - breast-feeding
- *Cautions*:
 - bilateral renal artery stenosis
 - aortic or mitral valve stenosis
 - hypertrophic cardiomyopathy
 - prior angioedema of any cause
 - hypotension (systolic blood pressure <90 mmHg)
 - patients on high-dose diuretics (i.e. furosemide >80 mg daily)
 - moderate to severe renal impairment (i.e. creatinine >150 $\mu\text{mol/L}$ or $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$)—seek specialist advice for initiation.

Initiation and target doses of commonly used ARBs

See Table 2.5.

Table 2.5 Indications and doses for commonly used ARBs

Agent	Starting dose	Target dose
Candesartan:		
Hypertension	8 mg daily	8–32 mg daily
Heart failure	4 mg daily	Aim for 32 mg daily if tolerated
Irbesartan		
	75–150 mg daily	Up to 300 mg daily
Losartan		
	50 mg daily	50–100 mg daily
Telmisartan		
	40 mg daily	Up to 80 mg daily
Valsartan:		
Hypertension	80 mg daily	Up to 320 mg daily
Post-MI heart failure	20 mg twice daily	Aim for 160 mg twice daily if tolerated

Monitoring

- Obtain baseline BP and U&Es before initiation
- Check BP and U&Es within two weeks of initiation or change of dose, then annually
- If serum creatinine increases by more than 20% (or eGFR falls by more than 15%) after initiation, stop ARB and seek specialist advice
- ARB dose should only be increased if:
 - systolic blood pressure >90 mmHg
 - serum creatinine increases by less than 20% (or eGFR falls by less than 15%) on each dose titration
 - potassium is <5.5 mmol/L.
- *Hyperkalaemia*: advise low-potassium diet, ensure adequate fluid intake. Reduce dose if $K^+ > 5.5$ mmol/L; withdraw ARB if $K^+ > 6$ mmol/L.

Adverse effects of ARBs

- *Symptomatic hypotension*: rare but may occur, particularly if there is intravascular volume depletion. Avoid excessive diuretic doses.
- *Angioedema*: has been reported rarely with ARBs. Particular caution should be taken when initiating an ARB in a patient with a history of angioedema of any cause.

Key ARB drug interactions

- *Ciclosporin*: increases risk of hyperkalaemia
- *Diuretics*: enhance hypotensive effect
- *Lithium*: increases lithium levels
- *Potassium supplements*: increased risk of severe hyperkalaemia.

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Aldosterone antagonists

(eplerenone, spironolactone)

Mode of action

The aldosterone antagonists are steroids that are structurally similar to aldosterone, a hormone that binds to mineralocorticoid receptors to promote sodium and water retention. Aldosterone increases blood pressure, promotes magnesium and potassium loss, potentiates the effects of the sympathetic nervous system, impairs the function of baroreceptors and endothelial function, and stimulates vascular fibrosis.

The aldosterone antagonists competitively bind to the aldosterone receptor to reduce sodium reabsorption and potassium excretion at the distal tubule and antagonize the effects of aldosterone listed above.

Clinical evidence

The landmark trial RALES (Randomized Aldactone Evaluation Study, 1999), secured the place of spironolactone in the management of severe heart failure (NYHA (New York Heart Association) class IV or class III with recent class IV exacerbation; ejection fraction (EF) < 35%), by demonstrating a 30% reduction in mortality and a 35% reduction in hospitalizations for heart failure, compared to placebo. In the EPHEUS (2003) study, eplerenone, initiated in patients with post-MI left ventricular dysfunction (EF < 40%) within 3–14 days of the acute event, demonstrated a 15% reduction in the risk of death over the course of one year.

Place in therapy

Heart failure: initially licensed at high doses (100–400 mg daily) to augment the effects of other diuretics in the treatment of congestive heart failure, spironolactone is now primarily used at low doses (25–50 mg daily) in patients with moderate to severe heart failure, as an adjunct to optimal ACE-I and β -blocker therapy for its prognostic benefits. Eplerenone may be considered as an alternative to spironolactone, under specialist supervision, for patients with severe left ventricular systolic dysfunction, where spironolactone is indicated but has not been tolerated, usually due to the development of gynaecomastia. This is an unlicensed use.

Post-MI heart failure: In line with NICE post-MI secondary prevention guidance, eplerenone should be prescribed within 3–14 days of MI, preferably after initiation of ACE-I therapy, for patients with symptoms and/or signs of heart failure and left ventricular septal defect (LVSD) with an EF \leq 40%.

Hypertension: Spironolactone is also indicated as an option at step 4 of the NICE/BHS (British Hypertension Society) hypertension treatment algorithm.

Compelling indications for aldosterone antagonists

- *Chronic heart failure*: spironolactone—as an adjunct to standard therapy (ACE-I, β -blocker plus diuretic) at low doses in patients with moderate to severe heart failure. Eplerenone may be considered as an alternative in patients unable to tolerate spironolactone first line (unlicensed)
- *Post-MI heart failure*: eplerenone—in patients with signs and symptoms of heart failure and reduced left ventricular systolic dysfunction. Start within 3–14 days of the event
- *Hypertension*: consider fourth line in patients with hypertension resistant to standard therapies (i.e. ACE-I, calcium-channel blocker, and thiazide diuretic).

Contraindications and cautions

- *Contraindications*: hypersensitivity to spironolactone or eplerenone, serum $K^+ > 5.0$ mmol/L at initiation, moderate to severe renal insufficiency, anuria, severe hepatic insufficiency
- *Cautions*: hepatic impairment (monitor electrolytes closely), renal impairment (avoid if eGFR < 50 mL/min, monitor electrolytes closely), pregnancy and lactation, elderly.

Target doses of commonly used aldosterone antagonists

See Table 2.6.

Table 2.6 Doses for commonly used aldosterone antagonists

Agent	Starting dose	Target dose
Spironolactone		
Heart failure	25 mg daily	50 mg daily ^a
Hypertension	100 mg daily	25–200 mg daily
Eplerenone	25 mg daily	50 mg daily ^a

Lower doses may be used in the event of hyperkalaemia (i.e. spironolactone 12.5 mg daily or 25 mg on alternate days). See Table 2.7.

Table 2.7 Recommended dose adjustments based on potassium levels

Serum K^+ (mmol/L)	Action	Dose adjustment
< 5.0	Increase dose	25 mg every other day to 25 mg daily 25 mg daily to 50 mg daily
5.0–5.4	Maintain dose	No dose adjustment
5.5–5.9	Decrease dose	50 mg daily to 25 mg daily 25 mg daily to 25 mg every other day 25 mg every other day to withhold drug
≥ 6.0	Withhold drug	

Following withdrawal due to hyperkalaemia, restart at a dose of 25 mg every other day if $K^+ < 5.0$ mmol/L.

Dosing

- *Chronic heart failure*: spironolactone is usually initiated at a dose of 25 mg daily, increasing to 50 mg daily after 4–6 weeks if the patient remains symptomatic. Dose reduction to 12.5 mg daily or 25 mg on alternate days may be required in the event of renal decline, hyperkalaemia, or hypotension.
- *Post-MI heart failure*: eplerenone should be initiated within 3–14 days of the acute event at a dose of 25 mg daily, increasing to 50 mg daily after 4 weeks.
- Doses of both spironolactone and eplerenone may need to be adjusted according to renal function and potassium levels.

Monitoring

- Check baseline blood chemistry and blood pressure.
- Check blood chemistry within a week (e.g. serum creatinine, urea, potassium, sodium) of starting therapy or dose adjustment and again after a month of therapy or dose adjustment.
- Monitoring is recommended at least 3 monthly thereafter.

Adverse effects of aldosterone antagonists

- *Hyperkalaemia*: this is common. Patients should be advised to avoid foods that are high in potassium—bananas, tomatoes, citrus fruit, Lo-Salt. Dose reduction, and in some cases drug withdrawal, may be necessary.
- *Renal dysfunction*: renal decline is common following initiation of spironolactone or eplerenone, particularly if already treated with ACE-I and diuretics. Careful control of fluid balance is essential. Dose reduction, and in some cases drug withdrawal, may be required.
- *Gynaecomastia*: some patients may tolerate minor swelling and discomfort; however, this frequently requires withdrawal of spironolactone. Eplerenone, free of effects on the progesterone receptor, may be considered as an alternative, although this is unlicensed in chronic heart failure.
- *Gastrointestinal*: diarrhoea, constipation, nausea, vomiting, and abdominal discomfort have been reported.
- *Menstrual irregularities*.
- *Rashes*.

Drug interactions with aldosterone antagonists

- *ACE-Is and ARBs*: increased risk of severe hyperkalaemia with aldosterone antagonists
- *Alpha-blockers*: enhanced hypotensive effect
- *Antiarrhythmic drugs*: plasma levels of eplerenone increased by amiodarone—reduce eplerenone dose
- *Antibacterial drugs*: plasma levels of eplerenone increased by clarithromycin and telithromycin—avoid concurrent use
- *Antidepressants*: plasma levels of eplerenone reduced by St Johns Wort—avoid concurrent use
- *Anti-epileptic drugs*: plasma levels of eplerenone reduced by carbamazepine and phenytoin—avoid concurrent use
- *Antifungal drugs*: plasma levels of eplerenone increased by itraconazole and ketoconazole
- *Antiviral drugs*: plasma levels of eplerenone increased by nelfinavir and ritonavir—avoid concomitant use; also by saquinavir—reduce eplerenone dose
- *Cardiac glycosides*: spironolactone may increase plasma levels of digoxin
- *Ciclosporin*: increased risk of hyperkalaemia
- *Lithium*: increased lithium levels with associated increased risk of toxicity
- *Potassium salts*: increased risk of hyperkalaemia
- *Tacrolimus*: increased risk of hyperkalaemia.

Beta-adrenoceptor blockers (β -blockers)

(e.g. atenolol, bisoprolol, metoprolol, nebivolol)

Mode of action

Beta-blockers block the action of noradrenaline at β -adrenoceptors, which are located in the myocardium, throughout the circulatory system and elsewhere. As a result, β -blockers inhibit sympathetic stimulation of heart rate and myocardial contractility. Beta-blockers slow the firing of the pacemaker cells in the sino-atrial node and hence are negatively chronotropic, and also affect the conduction through the atrioventricular (AV) node. Thus they also have anti-ischaemic and anti-arrhythmic effects. Beta-blockers lower blood pressure, although the exact mechanism for this effect is unclear. It is postulated that reducing circulating renin levels or lowering sympathetic tone may be responsible.

Clinical trial data

- **Angina:** IMAGE (International Multicenter Angina Exercise, metoprolol, 1992), APSIS (Angina Prognosis Study in Stockholm, metoprolol, 1996), TIBET (Total Ischaemic Burden European Trial, atenolol, 1996), ASIST (Atenolol Silent Ischaemia Study, atenolol, 1994)
- **Post-MI secondary prevention:** BHAT (Beta-blockers Heart Attack Trial, propranolol 1983), Norwegian Multicentre Study Group (timolol, 1981)
- **Heart failure:** CIBIS II (Cardiac Insufficiency Bisoprolol Study, bisoprolol), COPERNICUS (carvedilol), CAPRICORN (Carvedilol Prospective randomized Cumulative Survival, carvedilol), MERIT-HF (Metoprolol CR/XL Randomised Intervention trial in Congestive Heart failure, metoprolol), SENIORS (Study of the Effect of Nebivolol Interventions on Outcomes and rehospitalization in Seniors with heart Failure, nebivolol)
- **Atrial fibrillation:** limited data but summarized in NICE guideline CG36 *Atrial Fibrillation* (2006)
- **Hypertension:** meta-analyses have concluded that β -blockers do not confer the same stroke protection as other antihypertensive drugs, for the same degree of BP lowering. Beta-blockers are now no longer recommended early in the treatment of hypertension, unless there is another compelling indication to use them, i.e. post-MI, heart failure, or angina (NICE 2006).

Choice of agent

This should take into account the indication, the clinical trial data, and the properties of the individual β -blockers.

Key properties include:

- duration of action—longer-acting agents are preferred
- water or lipid solubility, which will influence adverse effects
- cardioselectivity.

See 'Compelling indications for beta-blockers',  p.111.

Dose

Optimal β -blockade is often described as control of resting heart rate to between 50 and 60 bpm.

Usual starting and target doses of β -blockers are listed in Table 2.8.

- For patients with borderline bradycardia, heart failure, or hypotension, on multiple antihypertensive therapy, or who are elderly, lower starting doses may be considered.

To ensure optimal cardioprotective effects, aim to titrate to the maximum tolerated dose.

Compelling indications for beta-blockers

- *Heart failure*: all patients with symptomatic heart failure and LVSD, initiated as early as possible following diagnosis in stable patients—*only bisoprolol, carvedilol and nebivolol are licensed in the UK*
- *Post-MI secondary prevention*: all patients following an MI, initiated during the inpatient phase of treatment
- *Angina*: first line for all patients with angina—aim to control resting heart rate to 50–60 bpm
- *Atrial fibrillation*: first line for patients in whom a rate-control strategy is appropriate.

Contraindications and cautions

- *Contraindications*:
 - asthma or history of bronchospasm*
 - second- or third-degree heart block
 - severe peripheral vascular disease
 - patients on verapamil.
- *Cautions*:
 - chronic obstructive pulmonary disease (if evidence of a reversible component)
 - uncontrolled heart failure
 - sick sinus syndrome
 - patients on diltiazem
 - hypotension or bradycardia <60 bpm
 - peripheral vascular disease
 - pregnancy and breast feeding.

Initiation and target doses of commonly used beta-blockers

See Table 2.8 and Table 2.9.

* Beta-blocker may be considered in heart failure under specialist supervision.

Table 2.8 Doses for commonly used β -blockers

Agent	Starting dose ^a	Target dose ^b
Atenolol	25–50 mg daily	50–100 mg daily
Bisoprolol	10 mg daily	10–20 mg daily
Bisoprolol in heart failure	1.25 mg daily	Increase slowly over 10–12 weeks aiming for 10 mg daily
Carvedilol	12.5 mg daily	50 mg daily
Carvedilol in heart failure	3.125 mg twice daily	Increase slowly over 10–12 weeks aiming for 25 mg twice daily
Metoprolol	25 mg twice daily	50–100 mg two to three times daily

Monitoring

- Obtain baseline BP and pulse before initiation and after dose changes.
- In the absence of side-effects review within 4 weeks and consider dose titration.
- Lethargy and/or impotence are not necessarily indications for drug withdrawal. Side-effects are frequently distressing but may wear off over time. Patient concerns should be addressed; however, they should be strongly encouraged to persevere with therapy in view of the cardiac benefits.
- If medication discontinuation proves necessary, withdraw β -blocker slowly to avoid reflex tachycardia.

Table 2.9 Characteristics of commonly prescribed β -blockers

Agent	Half-life (h)	Lipid solubility	Cardioselectivity
Atenolol	7	–	+
Bisoprolol	11	+	++
Carvedilol	6	+	–
Metoprolol	5	+	+
Nebivolol	10+	+++	+++

Adverse effects of beta-blockers

- *Bradycardia* (HR<50bpm): consider dose reduction, exclude heart block.
- *Symptomatic hypotension*: consider dose reduction, exclude heart block.
- *Bronchospasm*: review need for β -blocker and consider alternative drug class. If compelling indication, use a cardioselective β -blocker with extreme caution and under specialist supervision.
- *Fatigue*: may dissipate during therapy.

- *Cold extremities*: protect fingers and toes with gloves/socks in cold weather.
- *Sleep disturbances*: consider a water-soluble agent.

Key drug interactions with beta-blockers

- *Alpha-blockers*: enhanced hypotensive effect
- *Anti-arrhythmics*:
 - amiodarone—increased risk of myocardial depression, AV block and bradycardia
 - flecainide—increased risk of myocardial depression and bradycardia
 - lidocaine—increased risk of toxicity with propranolol
 - propafenone—increased plasma concentration of metoprolol and propranolol
- *Antidepressants*:
 - citalopram, escitalopram, paroxetine—increased metoprolol plasma concentration
 - enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs)
- *Antimalarials*: mefloquine—increased risk of bradycardia
- *Calcium-channel blockers*:
 - enhanced hypotensive effect
 - diltiazem—risk of AV block, bradycardia
 - verapamil—severe hypotension and heart failure
- *Ciclosporin*: increased plasma concentration with carvedilol
- *Clonidine*: increased risk of withdrawal hypertension
- *Diuretics*: enhanced hypotensive effect
- *Sympathomimetics*: adrenaline, dobutamine:—increased risk of severe hypertension and bradycardia with non-cardioselective β -blockers

Note: Sotalol, a β -blocker with class III anti-arrhythmic effects, has a number of specific interactions, which should be checked before prescribing.

Calcium-channel blockers (CCBs)

(e.g. dihydropyridine (DHP) type: amlodipine, felodipine, lacidipine, nifedipine; non-dihydropyridine (non-DHP) type: diltiazem and verapamil)

Mode of action

CCBs inhibit the inward movement of calcium ions through the slow channels located in the cells of the myocardium, the His–Purkinje system, and in vascular smooth muscle. The DHP-type CCBs have more affinity for the vascular smooth muscle, resulting in peripheral vasodilatation, reduced blood pressure, and reduced afterload, while the non-DHP type have more effect on the myocardial cells and conduction system, resulting in negative inotropy, myocardial depression, and AV conduction delay.

Clinical trial data

Hypertension: multiple studies demonstrate a significant reduction in mortality and morbidity, which are summarized in NICE CG34: *Hypertension* (2006).

Angina: reduce frequency and severity of angina episodes. As effective as β -blockers in protecting against effort-induced angina (APISIS, (verapamil, 1996)/TIBET (nifedipine, 1996). No end-point outcome data (mortality/morbidity) in stable or unstable angina, although verapamil and diltiazem are supported by studies indicating a reduction in events in post-MI patients.

Atrial fibrillation: verapamil, diltiazem—multiple small studies demonstrate efficacy in controlling heart rate at rest and during exercise, summarized in NICE CG36 *Atrial Fibrillation* (2006).

Choice of agent

DHP CCBs are usually used for the management of hypertension and as an addition to β -blocker to improve angina control. Non-DHP agents are chosen for the rate-control properties in angina, where β -blockers are contraindicated or not tolerated, and for the management of arrhythmias, particularly AF.

Care should be taken when prescribing, to choose the correct dose and formulation, particularly for diltiazem and nifedipine, with numerous dosing schedules depending on brand.

Dose

Usually the dose is titrated against response, aiming for adequate BP control in hypertension or a resting heart rate between 50 and 60 bpm in angina management. The starting doses and usual dose ranges of commonly prescribed CCBs are summarized in Table 2.10.

Compelling indications for CCBs

- *Angina:*
 - first line in patients where β -blockers are contraindicated or not tolerated—rate-controlling effects of diltiazem and verapamil may confer an advantage here
 - may also be used in combination with β -blockers (not verapamil), nitrates, nicorandil, or ivabradine (not diltiazem, verapamil)

- *Hypertension*: first line for older patients (>55 years) and black patients
- *Atrial fibrillation*: verapamil may be considered for rate control where first-line options have failed, or are contraindicated or not tolerated.

Contraindications and cautions

- *Contraindications*:
 - cardiogenic shock, advanced aortic stenosis, within one month of acute MI (AMI), unstable angina or acute coronary syndrome (ACS)
 - diltiazem, verapamil—AV block, severe bradycardia, left ventricular failure, sick sinus syndrome, and Wolff–Parkinson–White syndrome
- *Cautions*: worsening heart failure.

Initiation and dose range for CCBs

See Table 2.10.

Table 2.10 Doses for CCBs

Agent	Starting dose	Dose range
Amlodipine	5 mg daily	5–10 mg daily
Diltiazem	Dose depends on formulation and brand	
Felodipine	5 mg daily	5–20 mg daily
Lacidipine	2 mg daily	2–6 mg daily
Nifedipine	20–30 mg daily (LA preparation)	30–90 mg daily (LA preparation)
Verapamil	120 mg daily (LA preparation)	240–480 mg daily (La preparation)

CCB adverse effects

- *Bradycardia* (HR<50 bpm): (non-DHP only) consider dose reduction, exclude heart block.
- *Symptomatic hypotension*: consider dose reduction.
- *Flushing*: dissipates over time—encourage patient to persist with therapy.
- *GI disturbance*: may make constipation worse
- *Ankle oedema*: often dose related, consider dose reduction or combine with ACE-I or ARB
- *Gingival hyperplasia*: withdraw CCB and consider alternatives.

Monitoring CCBs

- Obtain baseline BP and pulse before initiation and after dose changes
- In the absence of side-effects review within 4 weeks and consider dose titration.
- Headache and flushing are common in the first week or two of treatment and usually resolve over time. Simple analgesics can be used to control headache if necessary. The patient should be reassured and encouraged to continue with therapy.
- Ankle swelling is common, especially with the DHP-type CCB at higher doses (i.e. after increasing from amlodipine 5 mg to 10 mg daily), and may limit the maximum dose.

Key drug interactions with CCBs

- *Alpha-blockers*: enhanced hypotensive effect
- *Anaesthetics*: enhanced hypotensive effect
- *Anti-arrhythmics*: non-DHP type: increased risk of bradycardia, myocardial depression with amiodarone and risk of asystole when verapamil given with flecainide/disopyramide
- *Anti-epileptics*: variable effects on plasma levels—consult product literature
- *Antifungals*
- *Antivirals*
- *Barbiturates*: effect of CCB reduced
- *Beta-blockers*:
 - enhanced hypotensive effect
 - diltiazem—risk of AV block, bradycardia
 - verapamil—severe hypotension and heart failure
- *Digoxin*: verapamil increases digoxin levels, with increased risk of AV block/bradycardia
- *Ciclosporin*: variable effects on plasma levels—consult product literature
- *Ivabradine*: plasma levels increased by diltiazem, verapamil—avoid concomitant use
- *Statins*: plasma concentration of simvastatin, atorvastatin increased by diltiazem/verapamil—reduce statin dose
- *Sirolimus*: plasma levels increased by diltiazem and verapamil
- *Tacrolimus*: plasma levels increased by diltiazem and nifedipine
- *Theophylline*: increased plasma levels of theophylline.

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Lipid-lowering therapies

Elevated concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) increase the risk of an individual developing cardiovascular disease. This is further exacerbated by low levels of protective HDL-C (high-density lipoprotein cholesterol) and elevated triglycerides. Five main classes of lipid-lowering drug therapies are used:

- statins
- fibrates
- cholesterol-absorption inhibitors
- bile acid binders (resins)
- nicotinic acid derivatives.

In terms of lowering cardiovascular risk, the wealth of evidence supports the use of statins in the first instance.

Aims of lipid-lowering therapies

The aims of lipid-lowering therapies remain a topic of much debate. National and international guidance is summarized overleaf, indicating the current disparity in the recommendations.

The optimal lipid profile is:

- TC <4 mmol/L
- LDL-C <2.0 mmol/L
- Triglycerides <1.7 mmol/L
- HDL cholesterol (HDL-C):
 - men >1.0 mmol/L
 - women >1.2 mmol/L

Lifestyle and blood pressure control alongside lipid lowering

The following lifestyle issues should be addressed alongside consideration of statin therapy:

- smoking cessation
- diet (reduce saturated fats, include Mediterranean diet and oily fish twice a week, aim for body mass index (BMI) of 19–25 kg/m², or a minimum of a 10% reduction in body weight)
- alcohol moderation to within safe limits (up to 21 units per week for men and 14 units per week for women)
- exercise (aim for a total of 30 minutes of moderate-intensity physical activity (e.g. brisk walking) at least 5× a week).

Blood pressure control

Treat if BP consistently over 140/90 mmHg to achieve a BP of less than 140/90 mmHg; more aggressive targets apply in patients with chronic kidney disease and diabetes.

Lipid targets in national and international guidelines

NICE (UK) 2008

- *Primary prevention*: generic statin only, no target lipid levels
- *Secondary prevention*: aiming towards TC<4 mmol/L and LDL-C<2 mmol/L
- *Type 2 diabetes*: treat to achieve TC<4 mmol/L and LDL-C<2 mmol/L
- *ACS*: high-intensity therapy aiming towards TC<4 mmol/L and LDL-C<2 mmol/L.

Joint British Societies-2 (UK) 2005

- Treat all individuals 'at high risk': atherosclerotic disease, diabetes, or at high total risk (CVD risk >20% over 10 years)
- Give lifestyle advice, monitor blood lipids, and treat to target: TC<4 mmol/L and LDL-C<2 mmol/L.

Examples of drug therapies that can affect the lipid profile

See Table 2.11.

Table 2.11 Drugs that affect the lipid profile

Drug	Effect
Alcohol	Increases HDL-C
Beta-blockers	Reduce HDL-C
Hormones:	
Androgens: testosterone	Increase LDL-C, reduce HDL-C
Oestrogens	Reduce LDL-C, increase HDL-C
Progestins	Increases LDL-C, reduce HDL-C
Immunosuppressants	
Ciclosporin	Increases LDL-C and HDL-C
Tacrolimus	Increases LDL-C and HDL-C
Steroids—glucocorticoids	Increase HDL-C
Thiazide diuretics	Increase LDL-C, reduce HDL-C

Lipid-lowering agents: statins (HMG-CoA reductase inhibitors)

(e.g. atorvastatin, pravastatin, rosuvastatin, simvastatin)

Statins block the action of the enzyme HMG-CoA reductase, which is responsible for catalysing the conversion of HMG-CoA to mevalonate. As a result, statins lower total cholesterol, LDL-C, apolipoprotein B, very low-density lipoprotein (VLDL), and plasma triglycerides. They also increase serum concentrations of HDL-C.

Clinical trial data

Consistent and robust clinical trials data support the role of statin therapy in cardiovascular (CV) risk reduction.

- *Primary prevention*: WOSCOPS (West of Scotland Coronary Prevention Study, 1995, pravastatin), AFCAPS/TexCAPS (Airforce/Texas Coronary Atherosclerosis Prevention Study, 1998, lovastatin), CARDS (Collaborative Atorvastatin Diabetes Study, 2004, atorvastatin), JUPITER (Justification for the Use of Statins in Primary Prevention, 2008, rosuvastatin)
- *Secondary prevention*: 4S (Scandinavian Simvastatin Survival Study, 1994, simvastatin), CARE (Cholesterol and Recurrent Events, 1996, pravastatin), LIPID (Long-term intervention with Pravastatin in Ischaemic Disease, 2000, pravastatin), HPS (Heart Protection Study, 2004, simvastatin), TNT (Treating to New targets, 2005, atorvastatin)
- ACS: MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering, 2001, atorvastatin), PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy, 2004, pravastatin vs. atorvastatin), A to Z (2004, simvastatin).

Suggested statin choice and dose

- *Primary prevention*:
 - initiate a generic statin, simvastatin 40 mg daily (or pravastatin 40 mg daily)
 - UK guidance (NICE) recommends no treatment targets for primary prevention
 - no routine dose escalation is recommended
- *Secondary prevention and diabetes*:
 - initiate a generic statin, simvastatin 40 mg daily (or pravastatin 40 mg daily)
 - intensify therapy in patients not achieving targets of TC > 4 mmol/L or LDL-C < 2 mmol/L, for example by switching to atorvastatin 40 mg daily or rosuvastatin 10 mg daily, and dose titrate if necessary
- ACS: initiate a high-intensity statin such as atorvastatin 80 mg daily
- *Familial hyperlipidaemia (FH)*:
 - initiate a generic statin, simvastatin 40 mg daily
 - switch to a high-intensity statin, such as atorvastatin 40 mg increasing to 80 mg daily, in patients not achieving the required 50% fall in LDL-C.

Average effect of statin therapy on the lipid profile

See Table 2.12.

Table 2.12 Effects of statin therapy on lipid profiles

Lipid element	Effect of statins
TC	reduced by ~30%
LDL-C	reduced by up to 40%
Triglycerides	reduced by ~20%
HDL-C	increased by ~6%

Potency of current statins on the UK market (mg to mg basis)

Fluvastatin < pravastatin < simvastatin < atorvastatin < rosuvastatin

Water-soluble statins

Pravastatin, rosuvastatin

Lipid-soluble statins

Simvastatin, atorvastatin, fluvastatin

Contraindications and cautions

- *Contraindications:*
 - hypersensitivity to the individual statin
 - Active liver disease (aspartate transaminase (AST) or alanine aminotransferase (ALT) level >100 iu/L) or unexplained persistent isolated elevations of serum transaminases
 - pregnancy and lactation
 - consideration should be given to delaying statin therapy or addressing contraceptive needs in women of child-bearing age
- *Cautions:*
 - hypothyroidism should be corrected before initiation of a statin
 - patients with a high alcohol intake
 - patients with risk factors for myopathy or rhabdomyolysis
 - acute porphyria (rosuvastatin is thought to be safe)
 - renal disease—dose reductions may be necessary.

Initiation doses and dose ranges

See Table 2.13.

Table 2.13 Doses for statins

Drug	Usual initiation dose	Dose range
Atorvastatin	10 mg daily (40 mg if switching from simvastatin 40 mg daily)	10–80 mg daily
Fluvastatin	20–40mg daily	20–80 mg daily
Pravastatin	Usually 40 mg once at night	10–40 mg daily
Rosuvastatin	5–10 mg daily (max 5 mg in Asian patients)	5–40 mg daily ^a
Simvastatin	Usually 40 mg daily—but lower dose if drug interactions	10–80 mg daily ^b

^a40 mg dose specialist use only.

^b80 mg dose recommended by NICE, but rarely used in clinical practice due to increased risk of myopathy.

Simvastatin

- Lipid-soluble agent; generic available
- Dose range: 10–80 mg daily
- Usual starting dose 40 mg daily; reduce if potential drug interactions or severe renal impairment
- Increased risk of myopathy at 80 mg dose, so generally avoided in clinical practice in favour of more potent agents
- First-line choice in most instances, except ACS and FH.

Pravastatin

- Water-soluble agents; generic available
- Dose range: 10–40 mg daily
- Usual starting dose 40 mg daily; limited in terms of potency
- Particularly useful at low doses in patients experiencing statin-related adverse effects with other agents; fewer drug interactions.

Fluvastatin

- Lipid-soluble agent; generic available
- Dose range: 20–80 mg daily
- Usual starting dose 40 mg daily; limited in terms of potency.

Atorvastatin

- Lipid-soluble agent; patented in Europe until 2011
- Dose range: 10–80 mg daily
- Usual starting dose: 20–40 mg daily unless ACS, where 80 mg daily should be initiated
- Usually used second-line to simvastatin in secondary prevention and first-line at high dose in ACS.

Rosuvastatin

- Water-soluble agent; patented in Europe until 2017
- Dose range: 5–40 mg daily (maximum dose of 20 mg in Asian patients)

- Starting dose: 10 mg daily, except Asians, where a lower starting dose of 5 mg is recommended
- 40 mg dose recommended only under specialist supervision
- Fewer drug interactions.

Adherence issues

- 50% of patients stop taking statin therapy within one year of initiation and 75% within three years.
- It is essential that patients understand the need for statin therapy to reduce their long-term risk of CV events, and that once initiated statins should be continued long term.
- Care should be taken to address adverse effects should they occur, in order to facilitate ongoing adherence.

In patients failing to respond to statin therapy, compliance issues should be suspected in the first instance and all efforts made to resolve these before switching to an alternative statin.

Dealing with statin-related adverse effects

- *GI disturbance*: advise patient to take with or after food—ideally with their evening meal rather than last thing at night.
- *Insomnia*:
 - try taking the dose earlier in the day, for example with the evening meal or earlier if necessary
 - try an alternative statin if the problem persists
- *Muscle aches and pains*:
 - check creatine kinase (CK) to exclude myopathy
 - if no increase in CK, withdraw agent and rechallenge. If problem recurs consider alternative statin
- *Myopathy*: muscle pains in the presence of a raised CK > 5 × ULN (upper limit of normal) indicates myopathy. Statin should be withdrawn and CK rechecked. Low doses of less-potent statins may be cautiously reintroduced with careful monitoring under specialist supervision.

Significant statin interactions

- *Anti-arrhythmics*: increased risk of myopathy when simvastatin given with amiodarone; maximum simvastatin dose = 20 mg
- *Antibacterials*:
 - clarithromycin—increases plasma concentrations of pravastatin and atorvastatin
 - clarithromycin, erythromycin, telithromycin—increase the risk of myopathy with simvastatin; avoid concurrent use
 - daptomycin—increased risk of myopathy with statins
 - fusidic acid—increased risk of myopathy with simvastatin
 - telithromycin—increased risk of myopathy with atorvastatin; avoid concurrent use
- *Anticoagulants*: caution with use of warfarin and other coumarins with atorvastatin, simvastatin, fluvastatin, rosuvastatin

- **Antifungals:**
 - itraconazole, ketoconazole, posaconazole, miconazole—increased risk of myopathy with simvastatin; avoid concomitant use
 - itraconazole, posaconazole—increase risk of myopathy with atorvastatin; avoid concomitant use
- **Antivirals:** use under specialist supervision only
- **Calcium-channel blockers:**
 - diltiazem, verapamil—possible increased in risk of myopathy with simvastatin; dose reduction required
 - diltiazem—increases plasma concentration of atorvastatin
- **Ciclosporin:** increased risk of myopathy with statins; dose reductions required; avoid concomitant use with rosuvastatin
- **Colchicine:** increased risk of myopathy with statins
- **Danazol:** possible increase in myopathy with simvastatin
- **Fibrates:** avoid concomitant use of statins with gemfibrozil; increased risk of myopathy when other fibrates are used with statins
- **Grapefruit juice:** plasma concentrations of simvastatin increased—avoid concomitant use; possible increase in plasma concentrations of atorvastatin with excessive intake
- **Nicotinic acid:** increased risk of myopathy with statins.

Monitoring

See Table 2.14.

Table 2.14 Monitoring of statin therapy

Lipid levels	<i>Primary prevention:</i> routine monitoring of lipid levels is not recommended, although clinicians should consider checking lipid levels occasionally throughout treatment to ensure ongoing adherence to therapy.
Total cholesterol (TC)	
High density lipoprotein (HDL)	<i>Secondary prevention:</i> lipid levels should be measured before therapy is initiated; at 12 weeks following initiation or change of dose; and at 12-monthly intervals thereafter.
Low density lipoprotein (LDL)	
Triglycerides	
Thyroid function tests (TFTs)	Check before initiating statin to exclude hypothyroidism.
Liver function tests (LFTs)	<p>Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12-monthly intervals thereafter.</p> <p>If transaminases $>3\times\text{ULN}$) discontinue statin and refer.</p> <p>For lesser increases in transaminases, which remain elevated at 6 months, consider specialist advice.</p>
Creatine kinase (CK)	<p>Baseline CK should be measured before starting a statin.</p> <p>CK should then only be measured during treatment when clinically indicated—i.e. where there are symptoms of muscle pain or tenderness, muscle weakness, or muscle cramps.</p> <p>Patients should be counselled on initiation of statin to report any usual muscle pain, tenderness, or weakness during treatment.</p> <p>IF MYOSITIS IS PRESENT OR SUSPECTED DISCONTINUE IMMEDIATELY.</p> <p>If muscle soreness occurs: rule out common causes (e.g. exercise), Check TFTs (hypothyroidism predisposes to myopathy), Measure CK:</p> <ul style="list-style-type: none"> ● if CK elevated $>5\times\text{ULN}$ stop and seek advice ● if CK elevated $<5\times\text{ULN}$ <ul style="list-style-type: none"> – monitor carefully by repeating CK level in one month – if remains elevated, reduce dose and recheck CK level in one month – if still remains elevated consider seeking advice – if symptoms continue, STOP statin and consult a specialist before re-initiating. <p>Note: Some black African and Caribbean individuals have elevated baseline levels of CK. This is not a contraindication to statin therapy. In these patients, after initiation, if the CK $>5\times$ baseline, seek advice.</p>

Other lipid-lowering agents

Fibrates

(bezafibrate, ciprofibrate, fenofibrate, gemfibrozil)

Mechanism of action

Fibrates act via a number of mechanisms including limiting substrate availability for triglyceride synthesis in the liver; promoting the effect of lipoprotein lipase resulting in increased LDL clearance; modulation of the LDL receptor/ligand interaction; and stimulation of reverse cholesterol transport. Fibrates lower triglycerides significantly, but also reduce LDL-C and TC levels, while increasing HDL-C.

Clinical trial data

Limited clinical evidence supports the use of fibrates to reduce CV events. The most recent study with fenofibrate in a diabetic population failed to demonstrate a benefit in the primary end-point of coronary events (coronary heart disease (CHD) death or non-fatal MI), but did show a small but significant reduction of 21% in CV events.

Dosing

Usual doses are as follows:

- *bezafibrate*: 400 mg once daily (MR prep)
- *ciprofibrate*: 100 mg daily
- *fenofibrate*: 160 mg daily (Supralip[®] preparation)
- *gemfibrozil*: 600 mg twice daily.

Place in therapy

The primary effect of fibrates on the lipid profile is a reduction in triglyceride levels. While fibrates may seem an obvious choice for the treatment of a patient with diabetes where raised triglycerides are often a problem, statins remain the first-line choice even for this group, due to the overwhelming trial evidence of benefit. Combination use of statins plus fibrates may be considered in patients requiring lipid lowering beyond monotherapy. However, the combination does increase the risk of myopathy and possibly rhabdomyolysis, and needs careful monitoring.

Hypertriglyceridaemia can be a problem in human immunodeficiency virus (HIV) patients taking protease inhibitors and statin–fibrate combinations may be useful in this group, under specialist supervision.

Adverse effects of fibrates

Key adverse effects include GI disturbances, which are usually self-limiting, and myositis. As with statins, drug interactions can be problematic. Particular care should be taken when co-prescribed with warfarin, due to an increased anticoagulant effect.

Impact of non-statin lipid lowering drugs on the lipid profile

See Table 2.15.

Table 2.15 Impact of non-statin lipid lowering drugs

	TC	LDL-C	HDL-C	Triglycerides
Fibrates	↓ ~15%	↓ ~20%	↑ ~10–15%	↓ ~40%
Cholesterol-absorption inhibitors	↓ ~ 15%	↓ ~20%	↑ ~ 3%	↓ ~ 8%
Bile acid sequestrants	↓ ~10%	↓ ~25%		May increase
Nicotinic acid		↓ ~ 15%	↑ ~ 15%	↓ ~ 45%

Key drug interactions with fibrates

- **Antibacterials:** increased risk of myopathy with daptomycin
- **Anticoagulants:** enhance effect of warfarin and other coumarins
- **Antidiabetic drugs:**
 - *rosiglitazone* levels increased by gemfibrozil—consider reducing *rosiglitazone* dose
 - increased risk of severe hypoglycaemia when gemfibrozil is given with repaglinide
- **Lipid-lowering drugs:**
 - increased risk of cholelithiasis and gall bladder disease when fibrates are used with ezetimibe—discontinue if suspected
 - increased risk of myopathy when fibrates are used with statin
 - avoid *concomitant* use of gemfibrozil and statins except under specialist supervision.

Cholesterol-absorption inhibitors

Currently only ezetimibe is on the market from this class.

Mode of action

Ezetimibe acts by interfering with the transportation of cholesterol across the brush-border in the GI tract, reducing delivery of intestinal cholesterol to the liver. The primary effect of ezetimibe on the lipid profile is a significant reduction in LDL, which is accompanied by a small reduction in triglyceride and an increase in HDL levels.

Clinical trial data

Despite the efficacy of ezetimibe in lowering LDL-C there remain no robust CV outcomes data to support this agent. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) data are due to report in 2012/13.

Dosing

The usual dose of ezetimibe is 10 mg once daily.

Place in therapy

Ezetimibe is primarily used as an adjunct to statin therapy when statin therapy alone does not deliver sufficient cholesterol lowering to achieve treatment targets. Ezetimibe may also be used as monotherapy in patients who are unable to tolerate statins first line.

Adverse effects

Key adverse effects include GI disturbances, headache, and fatigue. Myalgia can occur during therapy—check CK to exclude myopathy. Hypersensitivity reactions including rash, angioedema, and anaphylaxis have been reported.

Drug interactions

Although drug interactions are uncommon with ezetimibe, there is an increased risk of rhabdomyolysis when ezetimibe and statins are combined.

Key interactions are as follows:

- *Ciclosporin*: plasma concentrations of both drugs may be increased
- *Lipid-lowering drugs*: increased risk of myopathy and rhabdomyolysis when added to statins.

Bile acid sequestrants (resins)

(colestyramine, colestipol, and colesevelam)

Mode of action

Bile acid sequestrants reduce the enterohepatic circulation of cholesterol by preventing reabsorption from the gut. The fall in intestinal reabsorption increases LDL receptor activity in the liver, resulting in increased clearance of LDL from the plasma. The primary effect of bile acid sequestrants is therefore a reduction in LDL cholesterol levels, but the drugs can increase triglyceride levels, exacerbating hypertriglyceridaemia.

Clinical trial data

Cholestyramine showed a trend towards reduced mortality and non-fatal MI in the LRC-CPPT (Lipids Research Clinics Coronary Primary Prevention Trial, 1984); however, there are few other robust outcomes data to support this class. Colesevelam was launched in the UK in 2007 and may generate further CV outcomes data.

Dosing

Usual dosing is as follows:

- *colestyramine*: initially 4 g daily (max 36 g daily) in one to four divided doses. Each 4 g sachet must be mixed with at least 150 mL water
- *colestipol*: initially 5 g daily (max 30 g daily) in one or two divided doses. Each 5 g sachet must be mixed with at least 100 mL water
- *colesevelam*:
 - monotherapy—3.75 mg daily in one or two divided doses
 - with statin—2.5–3.75 mg daily in one or two divided doses

Place in therapy

Bile acid binders are limited in clinical practice by poor tolerability, drug interactions, and an adverse effect on triglyceride levels. Colesevelam, shows some promise in terms of improved efficacy and tolerability, although the possibility of drug interactions remains, and a negative impact on triglyceride levels has been established.

Adverse effects of bile acid sequestrants

Key adverse effects are GI, including constipation and diarrhoea, nausea and vomiting, and bloating.

Key drug interactions with bile acid sequestrants

- **Anticoagulants:** cholestyramine may increase or reduce the efficacy of warfarin and other coumarins.
- Bile acid sequestrants may affect the absorption of other drug therapies, including digoxin, thyroid hormones, fat-soluble vitamins (A, D, and K), and thiazide diuretics.
- As a result, other drug therapies should be taken at least 1 hour before or 4 hours after bile acid sequestrants, to reduce possible interference with absorption.

Nicotinic acid**Mode of action**

The exact mechanism of action by which nicotinic acid lowers cholesterol is unclear, but it is postulated that it disrupts the synthesis of triglycerides in the liver by blocking the enzyme DGAT-2, while also increasing the clearance of ApoA1. Nicotinic acid therefore primarily reduces triglyceride levels, with a moderate reduction in LDL-C, accompanied by a substantial increase in HDL.

Clinical trial data

Fifteen-year follow-up of the Coronary Drug Project (1986) indicated that nicotinic acid significantly reduced non-fatal MI and CHD death by a relative 14%.

Place in therapy

Limited outcomes data place nicotinic acid as an adjunct to statin therapy or as an alternative in patients unable to tolerate statins. Nicotinic acid may be particularly useful for patients with small dense LDL particles, high triglycerides and low HDL, a pattern frequently seen in patients with diabetes. However, as a molecule, nicotinic acid is poorly tolerated with a high incidence of facial flushing, which results in frequent treatment discontinuation. As a result, nicotinic acid has failed to deliver the outcomes demonstrated in the Coronary Drug Project in wider clinical practice.

Dosing

- **Nicotinic acid:** Niaspan[®] MR (modified release) prep—375 mg MR for one week, then 500 mg at night for one week, then 750 mg at night for one week then 1 g at night for one week. Increase by 500 mg at intervals of 4 weeks, to a maximum of 2 g daily.

Adverse effects of nicotinic acid

Common adverse effects include GI disturbance (nausea, vomiting diarrhoea, dyspepsia, abdominal pain), flushing, and rash.

Tredaptive[®]

(nicotinic acid plus laropiprant)

Tredaptive[®], a combination of nicotinic acid and an anti-flushing agent, laropiprant, was launched in 2009. Laropiprant, a prostaglandin inhibitor, suppresses prostaglandin-mediated flushing associated with nicotinic acid, without affecting its lipid-lowering efficacy. It is hoped that Tredaptive[®] will enhance adherence to therapy through improved tolerability. However, flushing is still reported in approximately 12% of patients on Tredaptive[®].

The impact of Tredaptive[®] on CV end-points is being assessed in HPS-THRIVE (Heart Protection Study: Treatment of HDL to Reduce the Incidence of Vascular Events), due to report in 2012.

Strategies to minimize flushing with nicotinic acid

- Start at a low dose and increase slowly in line with the dose titration schedule.
- Delay dose increases if necessary in patients experiencing significant flushing.
- Avoid drinking alcohol and hot drinks at the same time as taking the dose of nicotinic acid, as these will exacerbate the flushing side-effects.
- Consider the use of aspirin or a non-steroidal anti-inflammatory drug (NSAID), which can reduce the severity of flushing experienced—a single dose of aspirin 600 mg or ibuprofen 400 mg half an hour before taking the nicotinic acid dose is recommended.

Key drug interactions with nicotinic acid

- Lipid-lowering drugs: increased risk of myopathy when nicotinic acid is combined with statins.

Tredaptive[®] dose

- The usual dose of Tredaptive[®] is one MR tablet (1 g nicotinic acid/20 mg laropiprant) increasing to two tablets (2 g/40 mg) at four weeks.

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Nitrates

(glyceryl trinitrate (GTN), isosorbide mononitrate, isosorbide dinitrate)

Mode of action

Nitrates have powerful vasodilatory and venodilatory effects to improve coronary blood flow while reducing preload and afterload. Myocardial workload is therefore reduced, resulting in a reduction in myocardial oxygen demand. Nitrates protect against exercise-induced ischaemia by preventing coronary spasm and coronary arterial vasoconstriction induced by exercise.

Clinical evidence

Nitrates have been shown to reduce the frequency and severity of angina attacks if taken chronically at appropriate doses. Single dose of nitrates of between 15 mg and 120 mg have been shown to protect against effort-induced angina for up to 8 hours. Higher doses may be required to reduce angina frequency—one study using a longer-acting nitrate showed that only doses of 120–240 mg once daily had a significant effect on effort-induced chest pain.

Place in therapy

Sublingual GTN is used for the rapid symptomatic relief of angina, either for the relief of acute chest pain or prophylactically to prevent the development of predictable exertional chest pain.

Oral nitrates should be considered as adjunctive therapy in the prophylaxis of anginal chest pain. Nitrates may be added to β -blocker, calcium-channel blocker, or nicorandil therapy to improve symptom control.

Oral nitrates are generally not suitable as monotherapy, due to the problem of 'nitrate tolerance' (requiring a nitrate-free period) and the potential to precipitate reflex tachycardia.

Intravenous nitrates are used for the management of severe acute chest pain that is unresponsive to sublingual nitrates, and may be used to control blood pressure in acute situations.

Compelling indications for nitrates

- **Angina:**
 - rapid symptomatic relief of angina and for prophylactic use to prevent the development of predictable exertional chest pain
 - background anti-anginal therapy is indicated in all patients to prevent recurrence of chest pain, except those with very minimal and predictable symptoms that are manageable with sublingual nitrates alone. The BNF (*British National Formulary*) recommends initiation of anti-anginal therapy where attacks occur more than twice per week.

Contraindications and cautions

- **Contraindications:** nitrate hypersensitivity, aortic stenosis, hypotensive and hypovolaemic conditions, hypertrophic obstructive cardiomyopathy, cardiac tamponade, constrictive pericarditis, mitral stenosis, marked

anaemia, head trauma, cerebral haemorrhage. Concurrent sildenafil (Viagra[®]) therapy

- **Cautions:** hypothyroidism, closed-angle glaucoma.

Initiation and dose range for nitrates

See Table 2.16.

Table 2.16 Doses for nitrates

Agent	Dose
GTN	Tablets/spray: one tablet/spray (300–1000 mcg) under the tongue, repeat every 5–10 minutes. If chest pain does not resolve within 20 minutes, urgent medical advice should be sought Infusion: 10–200 mcg/min titrated to control chest pain. Maintain systolic blood pressure above 100 mmHg
Isosorbide mononitrate	Short-acting: 20–40 mg twice daily is commonly prescribed but may be subtherapeutic Long-acting formulations: 60–120 mg daily
Isosorbide dinitrate	Short-acting: 20–60 mg twice daily

Adverse effects of nitrates

- **Hypotension:** patients should be advised to sit down before taking sublingual nitrates. Significant hypotension and syncope can occasionally result.
- **Headache:** occurs due to cerebral vasodilatation. Can be reduced by spitting out the sublingual tablet after resolution of chest pain (sprays cannot be dealt with in this way). Simple analgesics (preferably paracetamol based) may be used.

Dosing

With short-acting nitrate formulations, dosing should be asymmetric (also referred to as eccentric) to allow for a nitrate-free period within each 24 hours. An interval of seven hours should be left between doses where a twice-daily regimen is prescribed (i.e. 8 am and 3 pm—nitrate levels will then fall overnight to reduce the risk of the patients developing nitrate tolerance).

Slow-release formulations release nitrate slowly over a period of 15–20 hours, allowing for a nitrate-free period within each 24 hours. These should not be prescribed twice daily for prophylaxis against angina, as nitrate levels will remain raised throughout the 24-hour period and efficacy will be significantly reduced. With the longer-acting formulations, doses of 120–240 mg have been shown to significantly reduce the frequency of angina attacks.

Monitoring nitrates

Little specific monitoring is required for patients taking nitrates, other than ensuring BP is maintained, with a systolic BP of >100 mmHg. The patient should be advised on managing nitrate-induced headaches and counselled carefully on asymmetric dosings if appropriate.

Key nitrate drug interactions

- *Anticoagulants*: infusion of GTN reduces the anticoagulant effect of heparins.
- *Sildenafil, tadalafil, vardenafil*: hypotensive effects of nitrates are significantly enhanced; avoid concomitant use.

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Potassium-channel activators

(nicorandil)

Mode of action

Nicorandil is a potassium-channel activator with a nitrate-like action. Opening of the potassium channel leads to arterial vasodilatation and reduced afterload, while the nitrate effect leads to venous dilatation and a reduced preload.

Clinical evidence

IONA (Impact of Nicorandil in Angina, 2002): this was designed to determine if nicorandil could reduce the frequency of coronary events in patients with chronic stable angina and standard anti-anginal treatment at high risk of cardiovascular events. The study reported a modest reduction in the composite primary end-point of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain (15.5% placebo vs. 13.1% nicorandil ($P = 0.014$)).

Place in therapy

Nicorandil is licensed for the prevention and long-term treatment of chronic stable angina and also for reducing the risk of acute coronary syndromes in patients with chronic stable angina and at least one of the following risk factors: previous MI or CABG, or CHD on angiography or a positive exercise test together with LVH on ECG, left ventricular dysfunction, age ≥ 65 years, diabetes mellitus, hypertension, or documented vascular disease. It is most frequently used as an adjunct to first-line anti-anginal therapies to provide additional symptomatic relief.

Dosing

A dose of 10 mg twice daily is recommended initially, reduced to 5 mg twice daily in patients who are predisposed to headaches. The dose should be increased gradually according to clinical response, to a maximum of 30 mg twice daily.

Monitoring nicorandil

- Blood pressure should be monitored at intervals during therapy.
- The drug dose should be adjusted to optimize symptomatic relief of angina episodes.

Compelling indications for nicorandil

- *Angina*: as an adjunct or alternative to first-line anti-anginal therapies to prevent angina episodes.

Contraindications and cautions

- **Contraindications:** cardiogenic shock, left ventricular failure with low filling pressures and hypotension, hypersensitivity to nicorandil, pregnancy and breast-feeding
- **Cautions:**
 - depleted blood volume, low systolic blood pressure, acute pulmonary oedema, or acute MI with acute left ventricular failure and low filling pressures
 - patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

Adverse effects of nicorandil

- **Headache:** occurs commonly, especially in the early phase of treatment; consider a lower starting dose
- **Dizziness and hypotension:** especially at higher doses
- **Peripheral vasodilation leading to flushing:** occurs commonly
- **Ulceration:** GI ulceration, skin ulceration, and ulcers of the mucosal membranes have been reported. These tend to be refractory to treatment and most only respond to withdrawal of nicorandil treatment
- **Angioedema:** occurs uncommonly.

Key drug interactions with nicorandil

- **Antihypertensives:** enhanced hypotensive effect with the addition of nicorandil
- **Oral corticosteroids:** increase of gastric erosions when used in combination with nicorandil; avoid concomitant use
- **Sildenafil, tadalafil, vardenafil:** due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

Ivabradine

Mode of action

Treatment with ivabradine causes a dose-dependent reduction in heart rate by selective and specific inhibition of the cardiac pacemaker I_f current (known as the funny channel) that controls spontaneous depolarization in the sinus node and hence regulates heart rate. The usual effect is a 10 bpm reduction in heart rate whether at rest or during exercise. The fall in heart rate leads to a reduction in cardiac workload and myocardial oxygen consumption.

Clinical evidence

Clinical studies have shown ivabradine to be as effective as β -blockers in the prevention and treatment of angina. The BEAUTIFUL (Morbidity–Mortality Evaluation of Ivabradine in Patients with CAD and Left Ventricular Systolic Dysfunction) study investigated the role of heart-rate control with ivabradine on top of background therapy, including β -blockers in the majority in patients with CHD and left ventricular failure. Ivabradine failed to demonstrate an impact on the primary end-point, a composite of cardiovascular death, hospitalization for acute MI, or hospitalization for new-onset or worsening heart failure. However, the study did confirm the safety of the combination of ivabradine and β -blockers. The SHIFT (Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine Trial) showed reduction of hospitalization and cardiovascular mortality in heart failure patients.

Place in therapy

Ivabradine was initially licensed for the symptomatic treatment of chronic stable angina in patients unable to tolerate, or with a contraindication to, the use of β -blockers; following the publication of the BEAUTIFUL study, the licence has been extended to include use in combination with β -blockers in patients who are inadequately controlled with an optimal β -blocker dose and whose heart rate is >60 bpm. In clinical practice, ivabradine is often used in patients that cannot tolerate either β -blockers or rate-controlling calcium-channel blockers on the basis of cost.

Dosing

- *Initiation:* ivabradine is usually initiated at a dose of 5 mg twice daily.
- After 3–4 weeks it may be increased to 7.5 mg twice daily if required for greater symptom control. If the patient is elderly or 5 mg twice daily is not tolerated, the dose can be reduced to 2.5 mg twice daily.

Monitoring ivabradine

- Obtain baseline BP and pulse before initiation and after each change in dose.
- In the absence of adverse effects, review within 4 weeks and consider increasing the dose if required for better symptom control.

Compelling indications for ivabradine

- *Angina*: as an adjunct or alternative to first-line anti-anginal therapies to prevent angina episodes.

Contraindications and cautions

- *Contraindications*: sick sinus syndrome, bradycardia (resting heart rate <60 bpm), cardiogenic shock and acute MI, within 4 weeks of CVA, sino-atrial block and third-degree AV block, congenital QT syndrome, pacemaker-dependent patients, unstable angina, pregnancy, and breast-feeding
- *Cautions*: pre-existing cardiac arrhythmias, concurrent heart-rate-lowering agents, mild heart failure (NYHA class I–II), moderate to severe heart failure (NYHA class III–IV—SHIFT study), post-CVA, retinitis pigmentosa, hypotension (avoid if BP <90/50 mmHg), hepatic insufficiency (avoid if severe), severe renal insufficiency (CrCl (creatinine clearance) <15 mL/min).

Adverse effects of ivabradine

- *Visual symptoms*: most commonly reported adverse effect. Luminous phenomena occurred in 15% of patients, and therefore new patients should be warned about this potential transient side-effect. The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night. Blurred vision has also been reported
- *Cardiac conduction effects*: bradycardia, AV 1st-degree block, ventricular extrasystoles can occur during therapy
- *Headache*: generally during the early treatment phase
- *Dizziness*: possibly related to bradycardia
- *GI disturbances*: nausea, vomiting, diarrhoea.

Key drug interactions with ivabradine

- *Antihypertensives*: enhanced hypotensive effect with the addition of nicorandil
- *Oral corticosteroids*: increase of gastric erosions when used in combination with nicorandil; avoid concomitant use
- *Sildenafil, tadalafil, vardenafil*: due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

Ranolazine

Mode of action

The mode of action of ranolazine is not well understood, despite the agent being in use in other countries for a number of years. Speculation on its mode of action focuses on inhibition of the late inward sodium current in cardiac cells. Reduced accumulation of sodium leads to a lower intracellular calcium load, facilitating myocardial relaxation and reducing diastolic stiffness. Ranolazine reduces the abnormalities of ventricular repolarization and contractility seen during episodes of ischaemia, with a resultant improvement in myocardial function and perfusion. The anti-anginal effects of ranolazine are independent of changes in blood pressure and heart rate.

Clinical evidence

Three placebo-controlled studies have confirmed the efficacy of ranolazine alone or as an adjunct to standard anti-anginal therapies (atenolol, amlodipine, or diltiazem) to improve symptomatic control in chronic stable angina (MARISA (Monotherapy Assessment of Ranolazine in Stable Angina), 2004; CARISA (Combination Assessment of Ranolazine in Stable Angina), 2004; ERICA (Efficacy of Ranolazine in Chronic Angina) 2006). MERLIN-TIMI-36 (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes—Thrombolysis in Myocardial Infarction), the only outcome study to date, investigated the use of ranolazine compared to placebo in the treatment of non-ST elevation in acute coronary syndrome, but failed to show an impact on the primary end-point of occurrence of CV death, MI, or recurrent ischaemia.

Place in therapy

Ranolazine is licensed and indicated as an adjunct to first-line anti-anginal therapies (such as β -blockers and/or CCBs) to improve symptomatic relief in patients with chronic stable angina. Due to cost, ranolazine is currently positioned as an adjunctive therapy where first- and second-line options are not tolerated or have failed to give adequate symptomatic relief. Ranolazine may also be particularly useful in patients with hypotension or bradycardia, as it has minimal effects on these haemodynamic parameters.

Dosing

- 375 mg slow release (SR) tablets twice daily initially, increasing after 2–4 weeks to 500 mg SR twice daily, and if necessary, to a maximum of 750 mg SR twice daily.

Monitoring

Blood pressure and pulse should be checked at baseline and within 4 weeks of initiation or dose change. Ranolazine usually has minimal effects on blood pressure and heart rate. ECG monitoring may be considered after initiation to ensure no significant QTc prolongation.

Small increases in serum creatinine have been noted during treatment, but this is not linked to renal toxicity.

Compelling indications for ranolazine

- *Angina*: as an adjunct or alternative to first- and second-line anti-anginal therapies to prevent angina episodes.

Contraindications and cautions

- *Contraindications*: severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$), moderate to severe hepatic impairment, pregnancy, and breast-feeding
- *Cautions*: initiate and undertake dose titration carefully in patients with mild to moderate renal impairment ($\text{CrCl} 30\text{--}80 \text{ mL/min}$), mild hepatic dysfunction, or moderate to severe heart failure (NYHA III–IV), elderly patients, and patients with low body weight ($>60 \text{ kg}$).

Adverse effects

- *Gastrointestinal*: diarrhoea, constipation, nausea, and vomiting occur commonly. Anorexia, reduced appetite, and dehydration occur uncommonly
- *Syncope, postural dizziness, headache*: may require dose reduction
- *Skin*: allergic dermatitis, urticaria, rash, pruritis, hyperhidrosis
- *Central nervous system (CNS)*: somnolence, tremor, fatigue. Rarely, disorientation, amnesia, depressed level or loss of consciousness
- *Eye and ear*: blurred vision, visual disturbance, vertigo, tinnitus.

Key drug interactions with ranolazine

- *Anti-arrhythmics*: avoid concomitant use with disopyramide
- *Antibacterials*: clarithromycin and telithromycin possibly increase ranolazine levels; avoid concomitant use. Rifampicin reduces ranolazine levels; avoid concomitant use
- *Antifungals*: ketoconazole, itraconazole, posaconazole, voriconazole increase plasma levels of ranolazine; avoid concomitant use
- *Antivirals*: possible increase in ranolazine levels; check individual agents for details
- *Beta-blockers*: avoid concomitant use with sotalol
- *Grapefruit juice*: may increase ranolazine levels; avoid concomitant consumption.

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Valvular heart disease

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General considerations

Development

Cardiac valves develop from the mesodermal germ layer between the 4th and 7th week of gestation. Any factors affecting embryogenesis during this time can affect development of valves and include infection (German measles/rubella), drugs, etc.

Key points

Mitral valve

- Two leaflets: anterior leaflet (is in fibrous continuity with aortic valve annulus) and posterior leaflet—competency depends on large-zone coaptation—supported by annulus, posteromedial and anterolateral papillary muscles coming off left ventricle (LV) free wall and septum, and tendinae chordae: changes in any of above can result in mitral regurgitation (MR).
- The posterior leaflet is divided into three segments by scallops; the anterior leaflet not scalloped—segments are based on which parts are opposite the posterior scallops, and each commissure is a segment, so P2 refers to the middle scallop of the posterior leaflet.
- The posteromedial papillary muscle is supplied by the circumflex or posterior descending coronary artery and is most prone to ischaemic rupture, causing flail posterior leaflet (compared to the anterolateral papillary muscle which has a dual supply).
- Posterior regurgitant jet is caused by posterior leaflet restriction (common) or anterior leaflet prolapse (unusual), and an anteriorly directed jet is due to posterior leaflet prolapse (most common) or anterior leaflet restriction (unusual). Central leaks come from annular dilatation. Eccentric jets often lead to commissural prolapse.

Aortic valve

- Trileaflet valve (right and left coronary cusps based on the location of the coronary ostia, and non-coronary cusp), with small-zone coaptation.
- Increase in size of annulus, sinuses, sinotubular junction, or leaflet destruction can result in aortic insufficiency (AI).
- Conduction tissue runs between the right and non-coronary cusp.

Tricuspid valve

- Three leaflets (septal, anterior and posterior) with a moderate zone of coaptation. The posterior and anterior annulus are most prone to dilatation.
- Atrioventricular (AV) node tissue is located just below the anteroseptal commissure.

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Acute rheumatic fever

Epidemiology

- <1:1000 in developed countries; 10:1000 schoolchildren in developing countries. It is rarer, but still accounts for half of cardiac disease in the developing world.
- Declining incidence is due to improved economic standards and housing, decreased crowding, and access to medical care and antimicrobials.
- Typically affects children aged 5–15 years from lower socio-economic class living in crowded conditions; 20% of cases are in adults. Incidence is higher in native Hawaiians and Maoris despite antibiotic prophylaxis.
- No sex difference but chorea and mitral stenosis (MS) are more common in females.

Pathology

- Typically occurs several weeks after a streptococcal pharyngitis. Usually group A beta haemolytic streptococci: *Streptococcus pyogenes* serotype M. Antigenic mimicry is implicated—antibodies to carbohydrate in cell wall (anti-M antibodies) of group A *Streptococcus* cross-react with protein in cardiac valves.
- Delay from acute infection to onset of rheumatic fever (RF) is usually 3–4 weeks. RF is thought to complicate up to 3% of untreated streptococcal sore throats. Previous episodes of RF predispose to further events (up to 50% of streptococcal sore throat is complicated by RF if there has been a previous episode). Other areas of cross-reactivity may explain other signs (e.g. involvement of connective tissue in joints—arthritis, caudate nucleus in brain—Sydenham's chorea).
- Commonly causes a pancarditis. Pericarditis can cause haemodynamic instability or constriction. Myocarditis may cause acute heart failure and arrhythmias. Endocarditis affects the mitral valve (65–70%), aortic valve (25%), and tricuspid valve (10%, never in isolation) causing acute regurgitation and heart failure, and eventually chronic stenosis.
- Pericardium, perivascular regions of myocardium, and endocardium develop perivascular foci of eosinophilic collagen surrounded by lymphocytes, plasma cells, and macrophages called Aschoff bodies.

Clinical features

- *Sore throat* 1–5 weeks earlier is reported in two-thirds of cases.
- Fever, abdominal pain, and epistaxis.
- Migratory large-joint *polyarthritis* starting in the lower limbs in 75% of cases. Duration less than 4 weeks at each site. Severe pain and tenderness in contrast to degree of joint swelling.
- *Pancarditis* in 50% of cases with features of acute heart failure, mitral and aortic regurgitation, an apical, mid-diastolic flow murmur (Carey Coombs murmur), and pericarditis.
- *Chorea* in 10–30%, usually 1–6 months after the index pharyngitis. Difficulty writing and speaking, generalized weakness, choreiform movements, and emotional lability. Joints hyperextended with hypotonia, diminished tendon reflexes, tongue fasciculation, and a

relapsing grip (alternate increases/decreases in tension). Recovery 2–3 months.

- *Erythema marginatum* is an evanescent rash with serpiginous outlines and central clearings on the trunk and proximal limbs. Seen in 5–13% of cases. Begins as erythematous, non-pruritic papules or macules that spread outwards. Fades and reappears in hours and persists.
- *Subcutaneous nodules* in 0–8% of cases several weeks after the onset of severe pancarditis. Mainly over bony surfaces or prominences and tendons. Commonly involves the elbows, knees, wrists, ankles, Achilles tendons, occiput, and vertebral spinous processes. Duration 1–2 weeks.
- There is a danger of overdiagnosing RF in children admitted with fever, soft murmurs, and arthralgia, all of which are common in childhood.

Treatment

See Table 3.1.

Table 3.1 Treatment of rheumatic fever

Drug/treatment	Dose
Antibiotics	Oral phenoxymethylpenicillin for 10 days (250 mg qds (four times a day) in children and 500 mg tds in adults)
	Or intramuscular benzylpenicillin (single dose of 1.2 million units) to treat the acute infection
	Oral erythromycin, if penicillin allergic, for 10 days (20–40 mg/kg/day qds in children and 250 mg qds in adults)
Alternatives include clarithromycin, azithromycin, or cefalexin	
Oral aspirin	4–8 g daily until erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are normal
Prednisolone	2 mg/kg/day for 2–4 weeks if moderate–severe carditis.
Oral haloperidol for chorea	0.5–2 mg tds in adults and 0.05–0.15 mg/kg/day in 3–12-year-old children
Use diuretics, angiotensin-converting enzyme inhibitors (ACE-Is), and digoxin for heart failure	
Surgery for chronic, severe rheumatic valve disease (results are less durable in acute phase)	

Prognosis

- Determined by level of cardiac involvement and antibiotic prophylaxis (5 years or until 21 years old if no carditis, 10 years or well into adulthood if carditis but no valve disease, 10 years or until 40 years old if valves affected and for all dental and surgical procedures).
- Acute phase duration about 3 months in 80% of cases. Mortality 1–10% in developing countries.
- Recurrence rates are high. Chronic valve disease occurs in one-third without and two-thirds with recurrent infections.
- Murmurs resolve in 50% of cases up to 5 years after index infection.

Diagnostic criteria for rheumatic fever (Jones criteria)**Evidence of group A streptococcal pharyngitis**

Either a positive throat culture or rapid streptococcal antigen test, or an elevated or rising streptococcal antibody titre (samples taken two weeks apart)

Plus two major or one major and two minor Jones criteria:**Major criteria**

- Polyarthritits
- Carditis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor criteria

- Fever
- Arthralgia
- Prolonged PR interval
- Elevated ESR and CRP

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Mitral stenosis: clinical features

Causes

Mitral stenosis (MS) is most commonly due to rheumatic fever. Other causes are rare. They include congenital (isolated lesion or in association with an atrial septal defect (ASD)—Lutembacher's syndrome), mitral annular calcification, carcinoid heart disease, valvulitis (systemic lupus erythematosus), mucopolysaccharidoses (e.g. Hurler's syndrome), and endocardial fibroelastosis. Stenosis occurs at three levels: the chordae (fuse, thicken, then shorten), cusps (initially rolled under edges, then thicken and eventually calcify), and commissures (progressive fusion).

Pathophysiology

Elevated left atrial (LA) pressure is required to propel the blood through the narrowed mitral valve orifice. This leads to pulmonary venous pressure and exertional dyspnoea due to pulmonary oedema and pulmonary compliance. Reactive pulmonary hypertension occurs leading to right ventricular (RV) hypertrophy and failure. LV function is initially unaffected. However, since filling is impaired, adequate cardiac output (CO) cannot always be maintained. The rise in CO during exertion is blunted. Onset of atrial fibrillation (AF) is associated with abrupt clinical deterioration, due to both the loss of atrial systole and the fast heart rate (decreased duration of diastole).

Clinical features (see also Fig. 3.1)

History

- Dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea.
- Acute pulmonary oedema may be precipitated by uncontrolled AF, exercise, chest infection, anaesthesia, and pregnancy.
- AF increases the risk of thromboembolism. Systemic embolism occurs in 20–30% and usually originates in the dilated LA and LA appendage.
- Fatigue is due to reduced cardiac output reserve and is common in mild–moderate stenosis.
- Haemoptysis can occur for a variety of reasons: alveolar capillary rupture (pink frothy pulmonary oedema); bronchial vein rupture (larger haemorrhage); blood-stained sputum of chronic bronchitis; pulmonary infarction (low CO, immobile patients).
- Chest pain similar to angina may occur in patients with pulmonary hypertension and RV hypertrophy, even with normal coronaries.
- Rarely, the enlarging LA may compress surrounding structures producing a hoarse voice (left recurrent laryngeal nerve compression—Ortner's syndrome), dysphagia (oesophageal compression), left lung collapse (left main bronchus compression).

Physical examination

Mitral facies or malar flush seen in <50%. Prominent 'a' waves in jugular venous pulse (JVP). Low-amplitude arterial pulse. Irregularly irregular pulse in AF. 'Tapping' apex beat—palpable S₁. Diastolic thrill at apex. Left parasternal heave (due to right ventricular hypertrophy (RVH)). Palpable pulmonary closure.

Auscultation: S_1 loud if in sinus rhythm and valve is pliable. P_2 accentuated. Opening snap (OS) of the MV is heard best at or medial to the apex in expiration. A_2 –OS interval varies inversely with severity of stenosis. Low-pitched, rumbling, mid-diastolic murmur with pre-systolic accentuation (if in sinus rhythm) is heard best at the apex with the patient in a left lateral position. Early diastolic murmur due to pulmonary regurgitation from pulmonary hypertension (Graham Steell murmur) may be heard rarely.

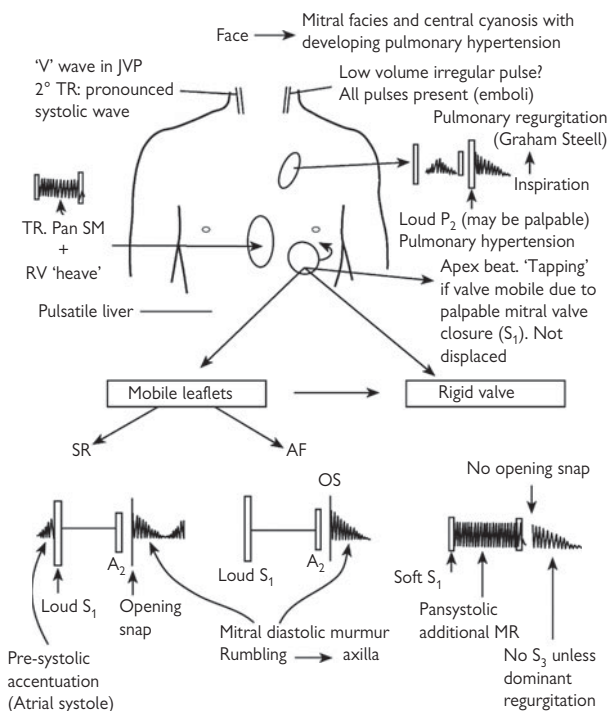


Fig. 3.1 Physical signs in mitral stenosis. Reproduced with permission from Swanton H (2003). *Pocket Consultant: cardiology*. 5th ed. Oxford: Blackwell Publishing. SM = systolic murmur; SR = sinus rhythm; TR = tricuspid regurgitation.


Mitral stenosis: investigations

Investigations

- **Electrocardiography (ECG):** P mitrale—bifid P wave (if in sinus rhythm) due to LA enlargement most prominent in lead II. Tall and peaked P waves in pulmonary hypertension. AF is frequent. Right-axis deviation and RV hypertrophy.
- **Chest X-ray (CXR):** Straightening of the left heart border, prominent upper lobe veins, pulmonary artery enlargement, Kerley B lines—interstitial oedema. Large LA visible as a double shadow.

Radiographic features of mitral stenosis

PA film	Lateral film
<ul style="list-style-type: none"> • Straight or convex L heart border • Double shadow of LA behind RA • Splaying of carina ($>90^\circ$)—rare • Dilated upper lobe veins • Prominent pulmonary conus • Pulmonary haemosiderosis 	<ul style="list-style-type: none"> • LA or RV enlargement • Valvular calcification frequent • LA calcification seen rarely (McCallum's patch) • Oesophageal indentation on barium swallow

- **Transthoracic ECHO (TTE):** Parasternal long-axis view (LAX) shows enlarged LA and doming of the valve leaflets due to commissural fusion. In short-axis view (SAX), the mitral valve orifice can be calculated by planimetry. Calcification can be visualized. M-mode imaging—restricted valve leaflet separation due to commissural fusion. Continuous wave (CW) Doppler can be used to estimate the valve area and transvalvular gradient (see  p. 15). Valve ECHO score can be calculated (based on leaflet mobility, leaflet thickening, subvalvular thickening, and calcification).
- **Transoesophageal echocardiography (TOE):** Provides better anatomic detail, can visualize small vegetations and thrombi in the LA.
- **Cardiac catheterization:** Increased pulmonary capillary wedge pressure (PCWP). Increased PCWP to LV end-diastolic pressure gradient. If the mean mitral gradient is low at rest, get the patient to perform exercise on the cath-lab table (e.g. straight-leg raising) to calculate gradient again. Assessment of co-existing coronary and valvular lesions.

Classification

See Table 3.2.

Table 3.2 Classification of mitral stenosis

Severity	Mean gradient (mmHg)	PA systolic (mmHg)	Valve area (cm ²)
Mild MS	<5	<30	>1.5
Moderate MS	5–10	30–50	1–1.5
Severe MS	>10	>50	<1

PA = pulmonary artery.

Management

Medical management

- Mild symptoms: salt intake restriction and oral diuretics (cautious).
- In AF: digoxin, β -blocker, or calcium-channel blocker for rate control. Restoration of sinus rhythm may be attempted if appropriate.
- Anticoagulation: recommended for those with AF, prior thromboembolism, or LA thrombus. Patients with low-output states, right heart failure, or LA dimension ≥ 55 mm by echocardiography should also be anticoagulated. There is no proven benefit if the patient is in sinus rhythm.
- Endocarditis prophylaxis is no longer recommended.¹

Balloon valvotomy

- Suitable for patients with pliable valves with minimal MR, no subvalvular distortion, and without heavy calcification (ideal if valve score ≤ 8).
- Contraindicated in moderate or severe MR or atrial thrombus.
- A guide wire is placed in the LA after trans-septal puncture, and a balloon (Inoue balloon) is directed across the valve and inflated at the orifice.

Indications for surgery

- Not indicated in asymptomatic patients
- In New York Heart Association (NYHA) III–IV patients:
 - mitral valve area (MVA) ≤ 1.5 cm² if valve not suitable for percutaneous mitral balloon valvuloplasty (PMBV)
 - MVA >1.5 but with pulmonary artery systolic pressure (PASP) >60 mmHg, PCWP ≥ 25 mmHg, or MV gradient >15 mmHg during exercise
- In NYHA I–II patients for MVA ≤ 1.5 cm² AND pulmonary artery systolic pressure (PASP) >60 – 80 mmHg if percutaneous mitral balloon valvotomy (PMBV) contraindicated.

Surgical treatment

- Indicated when morphology is not conducive to percutaneous balloon valvotomy (see algorithms in Figs 3.2 and 3.3).
- *Closed valvotomy*: fused cusps separated by a dilator introduced through LV apex. No longer recommended.

¹ Wilson W, Taubert KA, Gewitz M, et al (2007). Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* **116**(15): 1736–54.

- *Open valvotomy* with cardiopulmonary bypass is preferred to closed valvotomy. Cusps are separated under direct vision. Any fusion of subvalvular apparatus is loosened.
- *Mitral repair* is occasionally possible in advanced rheumatic stenosis using pericardium to augment leaflets, but durability is 5–10 years.
- *Mitral valve replacement* if repair is not possible:
 - 2–4% annual risk of major thromboembolic or haemorrhagic event, including stroke with mechanical valve (so very high lifetime risk in young patients), and small risk of reoperation for non-structural valve dysfunction
 - third-generation bioprosthetic valves' durability is dependent on age of patient—around 80% freedom from structural valve degeneration at 10 years in 40–50 year olds, versus over 90% freedom at 10 years in >65 year olds
 - surgical ablation for AF has 60–70% freedom from AF at one year: preoperative AF is not an indication for a mechanical valve.
- *Risk of surgery*: 1–2% mortality and stroke in 65-year-old patient with no other major morbidity and good LV function.

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Mitral stenosis guidelines

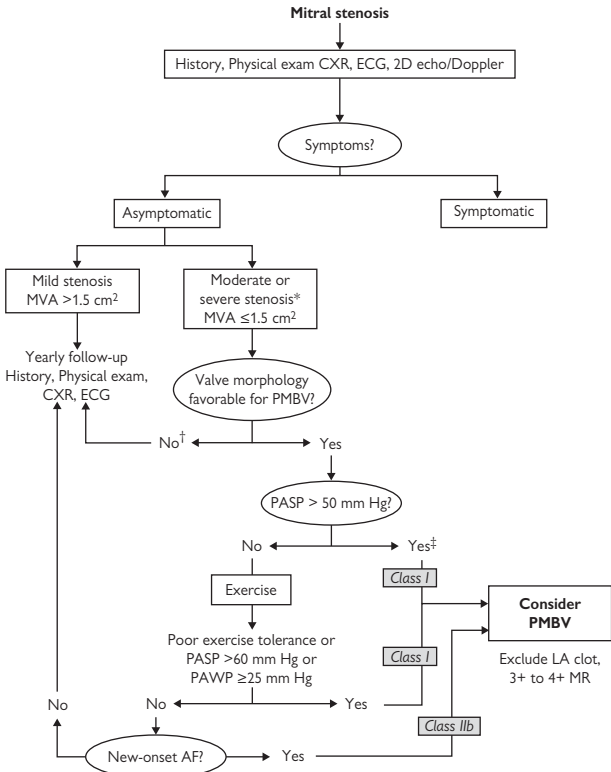


Fig. 3.2 Management strategy for patients with mitral stenosis. *The writing committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradients, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PASP) should also be taken into consideration. †There is controversy as to whether patients with severe mitral stenosis (MVA less than 1.0 cm^2) and severe pulmonary hypertension (pulmonary artery pressure greater than 60 mm Hg) should undergo percutaneous mitral balloon valvotomy (PMBV) or mitral valve replacement to prevent right ventricular failure. ‡Assuming no other cause for pulmonary hypertension is present. AF indicates atrial fibrillation; CXR, chest X-ray; ECG, electrocardiogram; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; and 2D, 2-dimensional. Reproduced with permission from *Journal of the American College of Cardiology*, Vol 48, No.3, 2006. August 1, 2006:e1–148. Bonow et al, AHA/ACC Best Practice Guidelines.

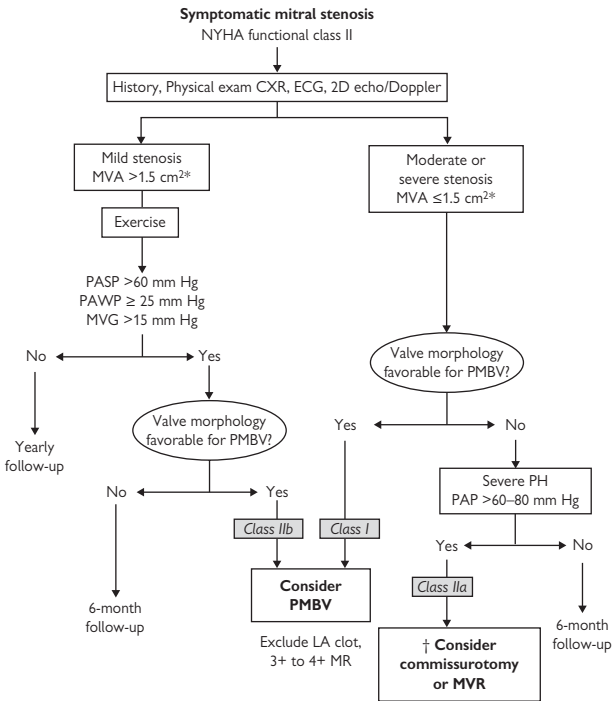


Fig. 3.3 Management strategy for patients with mitral stenosis and mild symptoms.

*The committee recognizes that there may be variability in the measurement of mitral valve area (MVA) and that the mean transmitral gradient, pulmonary artery wedge pressure (PAWP), and pulmonary artery systolic pressure (PASP) should also be taken into consideration. †There is controversy as to whether patients with severe mitral stenosis (MVA less than 1.0 cm^2) and severe pulmonary hypertension (PH; PASP greater than 60 to 80 mm Hg) should undergo percutaneous mitral balloon valvotomy (PMBV) or mitral valve replacement (MVR) to prevent right ventricular failure. CXR indicates chest X-ray; ECG, electrocardiogram; echo, echocardiography; LA, left atrial; MR, mitral regurgitation; MVG, mean mitral valve pressure gradient; NYHA, New York Heart Association; PAP, pulmonary artery pressure; and 2D, 2-dimensional. Reproduced with permission from *Journal of the American College of Cardiology*, Vol 48, No.3, 2006. August 1, 2006:e1-148. Bonow et al, AHA/ACC Best Practice Guidelines.

Mitral regurgitation

Causes

Acute: Infective endocarditis, acute myocardial infarction (MI), trauma.

Chronic: Most common—myxomatous degeneration (mitral valve prolapse), chronic rheumatic heart disease, left ventricular or annular dilatation of any cause (e.g. chronic ischaemia, cardiomyopathy, annular calcification), degeneration of valve cusps, collagen vascular disease, hypertrophic cardiomyopathy.


Nomenclature

- Essentially there is a spectrum of myxomatous degenerative disease from single-segment prolapse in small valves (fibroelastic deficiency) to multisegment prolapse in large valves (Barlow's disease).
- Mitral regurgitation (MR) can be classified by mechanism according to Carpentier's classification:
 - *type I*—normal leaflet motion, e.g. dilated annulus from dilated cardiomyopathy, leaflet perforation due to endocarditis
 - *type II*—leaflet prolapse, e.g. myxomatous degeneration
 - *type IIIa*—restricted leaflet opening, e.g. rheumatic disease
 - *type IIIb*—restricted leaflet closing, e.g. ischaemic dilated cardiomyopathy (functional).

Pathophysiology

- Damage to leaflets, chordae, papillary muscles, or LV can cause MR.
- The LV ejects into the LA during systole, as well as antegrade into the aorta.
- In acute MR:
 - there is little enlargement of the LA due to normal compliance. This results in raised LA pressure and can result in pulmonary oedema
 - there is no compensatory LV enlargement, so the forward ejection fraction (EF) is reduced, leading to low CO.
- In longstanding severe MR, there is enlargement of the LA, which accommodates the volume overload with minimal rise in LA pressure. The LV dilates, and large stroke volume compensates for regurgitation, maintaining the forward EF. LV failure results from longstanding volume overload. The low-pressure regurgitant pathway masks LV failure: EF is often normal even when LV is very impaired.

Clinical features

In acute severe MR—pulmonary oedema is common, hypotension, cardiogenic shock. This is a medical emergency. See  p. 728.

History

- Chronic MR—initially asymptomatic. Fatigue (due to ↓ forward CO), exertional dyspnoea, orthopnoea, systemic embolization (less common than MS). Palpitations (↑ stroke volume/associated AF). Right heart failure in later stages
- Symptoms and risk factors of endocarditis, ischaemic heart disease.

Physical examination

Rapid upstroke in arterial pulse. Irregularly irregular pulse in AF. Prominent 'a' waves in JVP in patients in sinus rhythm. Large 'v' waves if there is associated tricuspid regurgitation (TR). Forceful apex displaced laterally (LV dilatation). Systolic thrill at apex.

Auscultation: Pansystolic murmur loudest at the apex and radiating into the axilla. Soft first heart sound. Loud mitral valve closure sound helpful in excluding severe MR. Wide splitting of S_2 due to premature aortic valve closure. Prominent low-pitched S_3 . A mid-diastolic flow murmur may follow S_3 even in the absence of MS.

Investigations

- **ECG:** LA enlargement, left ventricular hypertrophy (LVH), RA enlargement in pulmonary hypertension. AF common in chronic MR.
- **CXR:** Cardiomegaly, LA and LV enlargement, and pulmonary venous congestion. Calcified mitral annulus may be seen.
- **TTE:** Demonstrates MV anatomy (lesion and type of MR). Colour Doppler to detect and quantify the MR (Table 3.3). Assessment of LV function from EF, end-systolic dimension and end-diastolic dimension (**Note:** In compensated MR, EF is always overestimated because of the low-resistance retrograde pathway).
- **TOE:** Shows the anatomy in greater detail and allows accurate assessment of the feasibility of valve repair. Should be performed pre- or intra-operatively.
- **Cardiac catheterization:** Not always required. Ventriculogram can quantify MR severity and EF. Detection of co-existing valve lesions and coronary artery disease.

Classification of organic mitral regurgitation

See Table 3.3.

Table 3.3 Classification of mitral regurgitation

Severity	Angiographic grade	Jet area (% of LA area)	Jet width (cm)	Regurgitant fraction (%)	ERO (cm ²)
Mild MR	Contrast seen entering LA	<20	<0.3	<30	<0.2
Moderate MR	Contrast in LA same intensity as LV within 3–4 beats	20–40	0.3–0.69	30–49	0.2–0.39
Severe MR	Contrast in LA same intensity as LV within 3–4 beats	>40	≥0.7	≥50	≥0.4

ERO = effective regurgitant orifice.

Prognosis

Prognosis depends upon the aetiology of MR (e.g. ischaemic MR confers significantly worse prognosis). Outcome is poor in symptomatic severe MR; 33% survival at 8 years without surgical intervention. Death occurs mostly from heart failure but there is a substantial incidence of sudden death, which may be arrhythmia related.

Mitral regurgitation guidelines

Management

Medical management

- Although at increased risk for endocarditis, in the 2008 update to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, routine prophylaxis is no longer recommended.
- Asymptomatic patients with mild MR are managed conservatively with serial echocardiograms.
- Vasodilators in symptomatic patients to increase forward CO and reduce regurgitant volume.
- In AF: rate control and anticoagulation (goal international normalized ratio (INR) 2–3). Note: new-onset AF is a class IIa indication for surgery in chronic, severe MR.

Surgical treatment

- Indicated for patients with severe MR who are symptomatic despite optimum medical management.
- Asymptomatic patients with severe MR may need surgery if there is:
 - worsening of LV function (EF 30–60% or LV end-systolic dimension ≥ 40 mm)
 - new AF
 - pulmonary hypertension.
- Mitral valve repair is strongly preferred to valve replacement: it is the only intervention that restores life expectancy to normal, and offers event-free survival that is superior to medical management or replacement.
- Likelihood of repair is highly dependent on surgeon expertise.
- Repair minimizes risk of haemorrhage and thromboembolism, reoperation, LV dysfunction, and endocarditis.
- Multisegment prolapse, and heavily calcified valves, are more difficult to repair than single-segment prolapse, and non-calcified valves.
- Percutaneous MV repair methods (edge-to-edge mitral clip and coronary sinus annuloplasty band) are currently being tested, but are not yet approved.
- *Risk of surgery:* 1–2% mortality and stroke in 65-year-old patient with no other major morbidity and good LV function. Ischaemic MR and endocarditis risk rises to around 2–5%.

Further reading

European Society of Cardiology (ESC) (2007). Guidelines on the Management of Valvular Heart Disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* **28**: 230–68. <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-VHD-FT.pdf>

Mitral valve prolapse

- **Definition:** Systolic billowing of one or both MV leaflets above the plane of the MV annulus into the LA
- Nomenclature is confused: MV prolapse may result in MR, and is almost always due to degenerative disease (also known as ‘floppy valve’ or myxomatous degeneration), and occasionally connective tissue disorders. There is a spectrum of degenerative disease which includes Barlow’s disease (multisegment prolapse in giant valves) and fibroelastic deficiency (single segment prolapse in small valves). These terms are often used interchangeably.
- **Prevalence:** 0.6–2.4%. ♂ > ♀

Causes

Most cases are idiopathic. Connective tissue disorders including Marfan’s syndrome, Ehlers–Danos syndrome, pseudoe xanthoma elasticum, osteogenesis imperfecta. Present in 20% of ostium secundum ASD.

Pathophysiology

Myxomatous degeneration and excess mucopolysaccharides lead to thickened, enlarged valve leaflets, in one or more segments. Prolapse results from elongated or ruptured chordae tendinae and excess leaflet tissue. MV leaflet (usually posterior—P2 segment) prolapses into the LA during ventricular systole.

Clinical features

Mostly asymptomatic. Atypical chest pain, Palpitations resulting from ventricular and supraventricular arrhythmias. Symptoms of MR if significant.

Mid or late systolic click due to tensing of the chordae tendinae and prolapse of the leaflet. Late systolic murmur due to associated MR.

Investigations

ECG is usually normal. Some non-specific changes may be seen. CXR is normal if there is no significant MR on TTE. Systolic displacement of one or both MV leaflets by >2 mm into the LA beyond the high points of mitral annulus. Assessment of MR.

Management

Infective endocarditis prophylaxis no longer recommended.¹ Beta-blocker for chest pain and palpitations. Anticoagulation if in AF or prior thromboembolic event. MV repair (rarely replacement) for severe MR (surgical indications same as for MR).

¹ Wilson W, Taubert KA, Gewitz M, et al (2007). Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* **116**(15): 1736–54.

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Aortic stenosis

Incidence

Commonest valve lesion in UK. $\sigma^{\circ} > \text{♀}$. \uparrow with age. 2% of people >65 years have ECHO features of aortic stenosis (AS). Congenital bicuspid AS presents ~ 20 years earlier. Becoming more common (population aging, improved diagnosis).

Causes

Acquired: Degenerative calcific AS (commonest); rheumatic fever, Paget disease of bone, end-stage renal failure, ochronosis.

Congenital: Bicuspid aortic valve 1–2% live births. Bicuspid AV results in chronic turbulent flow, which results in calcification and fibrosis of leaflets with reduced valve area.

Pathogenesis

AS can occur at the level of the valve or above (supravalvular stenosis) or below (subvalvular) the aortic valve. Degenerative calcific AS results from years of normal stress on the valve. Similar risk factors as ischaemic heart disease (IHD) (\uparrow blood pressure (BP), \uparrow lipids, diabetes mellitus (DM)). Inflammatory change occurs within the valve, with calcium deposited along flexion lines causing immobility, reduced excursion, and reduced opening area. Rheumatic AS is due to adhesion and fusion of commissures, with fibrosis and retraction.

Pathophysiology

Progressive narrowing of the valve orifice results in compensatory LVH to maintain stroke volume. LVH results in a stiff, non-compliant ventricle with elevated end-diastolic pressure (diminished coronary perfusion pressure). Atrial component of LV filling then becomes more significant. Pressure overload eventually results in LV failure (pulmonary oedema, low cardiac output) and fall in transvalvular gradient because of reduced EF through valve.

Clinical features

History

- Classical triad: angina, syncope, dyspnoea
- Angina pectoris: from \uparrow O₂ demand due to LVH and increased wall tension (\downarrow subendocardial perfusion). Occurs in $2/3$ —only $1/2$ of these have obstructive coronary lesions
- Syncope: on exertion cannot increase CO in setting of peripheral vasodilation leading to \downarrow cerebral perfusion
- Dyspnoea: pulmonary oedema causing dyspnoea (exacerbated by AF).
 - sudden death from ventricular arrhythmias
 - acquired von Willebrand disease and platelet dysfunction in patients with severe AS due to shearing of von Willebrand factor (VWF) multimers and platelets.

Physical examination

Slow-rising, small-volume pulse (pulsus parvus et tardus)—best felt at carotid. BP—narrow pulse pressure, in advanced AS systolic BP is \downarrow .

Prominent 'a' wave on JVP. Sustained, heaving apical impulse. If congestive cardiac failure (CCF) develops, the apex beat is displaced inferolaterally. Systolic thrill is felt in the aortic area (2nd intercostal space on right) during full expiration.

Auscultation: S_1 normal or soft. In mild AS, S_2 normal (i.e. A_2 precedes P_2). In moderate AS, S_2 becomes single (closure of AV delayed until it coincides with closure of PV). In severe AS, there is paradoxical splitting with A_2 after P_2 . S_4 is often heard (atrial contraction into stiff ventricle) and systolic ejection click (if valve pliable). Mid-systolic crescendo–decrescendo ejection murmur is heard throughout precordium but best heard at right upper sternal border in full expiration. Radiates to carotids. As AS severity worsens, the murmur peaks later, extends later through systole, and may obscure S_2 .

Investigations

- **ECG:** LVH with strain; left bundle branch block (LBBB), left atrial enlargement (LAE).
- **CXR:** calcification in valve or aortic root, post-stenotic dilatation in ascending aorta.
- **TTE:** calcified valve with restricted opening (M-mode). Colour Doppler to detect concomitant aortic regurgitation (AR). CW Doppler to assess velocity (and hence gradient) across valve (see [Fig. 14.1](#) Transthoracic Doppler imaging, p. 14). Determine AV area and EF.
- **Cardiac catheterization:** mainly to assess for concomitant coronary artery disease prior to aortic valve surgery (present in 50% with calcific AS). No need to assess pullback gradient across valve nowadays (significant risk of embolic events with this, CW Doppler accurately assesses gradient and LV function).
- **Dobutamine stress:** in patients with severe AS and low EF/low gradient to detect myocardial reserve and differentiate true stenosis with secondary LV dysfunction from pseudostenosis (low gradient from moderate AS and low CO from myocardial disease unrelated to valve lesion). In pseudostenosis, measured AV area will \uparrow with dobutamine).

Classification

See Table 3.4.

Table 3.4 Classification of aortic stenosis

Severity	Jet velocity (m/s)	Gradient (mmHg)	AV area (cm ²)
Mild AS	<3	<25	>1.5
Moderate AS	3–4	25–40	1–1.5
Severe AS	>4	>40	<1

Prognosis

Rate of progression is highly variable, although AV area is estimated to decrease approximately 0.1cm^2 per year. Symptoms are often not present until AS is severe (gradient across valve often >100 mmHg). Once symptoms occur, prognosis significantly worsens without surgical intervention.

- Patients who present with angina have a 5-year mean survival.
- Patients who present with syncope have a 3-year mean survival.
- Patients who present with dyspnoea due to CHF have a 2-year mean survival.

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Management of aortic stenosis

Medical management

- No medical treatments are proven to prevent or delay the disease process in the AV leaflets.
- There is no effective medical treatment to improve prognosis:
 - β -blockers reduce myocardial O_2 demand and may improve coronary blood flow
 - cautious use of loop diuretics may relieve preload and help with dyspnoea (avoid hypovolaemia)
 - in CHF or dilated LV, digoxin may help with dyspnoea (particularly if patient is in AF/flutter)
 - in severe AS, avoid negative inotropes and drugs that reduce afterload (e.g. glyceryl trinitrate (GTN), angiotensin-converting enzyme inhibitors (ACE-Is)), as these may worsen the gradient and cause syncope.

Surgical treatment

- Surgery is the treatment of choice for symptomatic AS.
- Acute decompensation of severe AS is a medical emergency.
- In asymptomatic severe AS, $EF < 50\%$ (see algorithm opposite).
- Aortic valve replacement (AVR) is reasonable for asymptomatic moderate or severe AS when undergoing concomitant coronary artery bypass graft (CABG), aortic, or valve surgery.
- AVR is a safe effective procedure (surgical mortality 1%, complication rate thereafter 1%/year cumulative in large-volume centres, but national registries report mortality around 3%).
- Bioprosthetic valves are preferred in older patients as they have excellent freedom from structural valve degeneration, and may be used in younger patients who want to avoid the 2–4% linearized annual risk of thromboembolic or haemorrhagic stroke.

Balloon aortic valvuloplasty

- Introduced as non-surgical alternative treatment for AS.
- Prognosis same as for medical management because of procedural complications (~3% mortality and ~6% MI/severe AR/myocardial perforation) and restenosis rates (50% restenosis within 3–6 months):
 - children/adolescents with non-calcified AS.
 - patients deemed unfit for AVR or who refuse surgery.
 - bridge to transcatheter aortic valve replacement (TAVI)/AVR (treat acute decompensation so patient can be optimized before surgery).

Transcatheter aortic valve replacement

- TAVI is approved in Europe and is currently undergoing phase III clinical trials in the United States.
- Pericardial valves mounted on expandable stents may be placed in the aortic position via the transfemoral or transapical routes, after a balloon is expanded inside the stenotic valve.

- Increased experience and technological improvements have led to low procedural morbidity and mortality, with good early results suggesting survival superior to that of medical management or balloon valvuloplasty.

Further reading

European Society of Cardiology (ESC) (2007). Guidelines on the Management of Valvular Heart Disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* **28**: 230–68. <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-VHD-FT.pdf>

Aortic regurgitation

Causes

Valvular: Rheumatic heart disease (often combined with AS as well as MS/MR), infective endocarditis, degenerative calcific (with AS), bicuspid aortic valve, trauma. **Aortic root disease:** Hypertension, aortic dissection, Marfan's syndrome. Other causes are rare: osteogenesis imperfecta, syphilitic aortitis, spondyloarthritis (ankylosing spondylitis, Reiter's, etc.), arteritis (Takayasu's, giant cell).

Incidence

Less common than AS. Valvular causes are becoming less frequent and aortic root causes now account for >50% of cases.

Pathogenesis

Valvular disease: Valvular fibrosis and fusion of cusps results in retraction of cusps such that they cannot coapt properly.

Subacute bacterial endocarditis (SBE): Direct destruction of valve cusps/vegetations.

Aortic root disease: Progressive dilatation of aortic root causes failure of coaptation of cusps and regurgitation.

Pathophysiology

As the valve fails, more of the LV stroke volume regurgitates into the LV. CO is maintained by compensatory LV dilatation and hypertrophy increasing stroke volume but at the expense of increasing end-diastolic volume. Volume overload leads to eccentric hypertrophy, myocyte function deteriorates, and further LV dilatation occurs, leading to LV decompensation.

Clinical features

In acute AR, dyspnoea is common (\uparrow forward CO in a setting of non-compliant LV (\downarrow left ventricular end-diastolic pressure (LVEDP)) leads to pulmonary oedema, hypotension, and cardiogenic shock. Acute AR is a medical emergency.

History

- In chronic AR, initially asymptomatic. LVEDP is low due to LV dilatation. Chronic volume overload leads to LV failure and CHF.
- Angina, symptoms of aortic dissection (e.g. chest pain radiating to back).
- Ask about symptoms of endocarditis.

Physical examination

Wide pulse pressure: collapsing (water-hammer) pulse, Corrigan's sign (visible carotid pulsation), De Musset's sign (head nodding with each pulse), Müller's sign (visible pulsation of uvula), Traube sign ('pistol shot femorals'—loud bruit heard with stethoscope over femoral artery), Quincke sign (visible capillary pulsation in nailbed), Duroziez sign (systolic and diastolic bruits heard over femoral artery when artery is digitally compressed).

Apex beat displaced inferolaterally and diffuse/hyperdynamic. May feel apical systolic thrill. **Auscultation:** A_2 may be normal (or louder) if AR is due to aortic root pathology, and may be soft or absent if AR is due to aortic valve pathology. S_3 may be heard with dilated LV or with incipient failure. An ejection systolic murmur (ESM) similar to AS may be audible (either due to mixed AR/AS or due to turbulent flow due to \uparrow stroke volume (SV)). Murmur of AR is a high-pitched, early-diastolic decrescendo murmur immediately following A_2 . Best heard with patient sitting up and leaning forward in expiration. Heard most clearly along the left upper sternal border (occasionally along right sternal border if aortic root dilated). Duration of murmur in diastole correlates with severity of AR. Austin Flint murmur is a mid-diastolic murmur heard at apex due to antegrade flow across a mitral valve orifice which has been narrowed by a combination of rising LV pressure and jet of AR directed at the anterior MV leaflet.

Investigations

- **ECG:** LVH with strain, left axis deviation.
- **CXR:** in chronic AR there is enlarged cardiac shadow. Dilated ascending aorta with aortic root pathology.
- **TTE:** colour Doppler and CW Doppler confirm diagnosis and assess severity. M-mode measures aortic root and LV dimensions, EF.
- **Cardiac catheterization:** to assess for concomitant coronary artery disease prior to aortic valve/root surgery. Aortogram in left anterior oblique (LAO) projection shows aortic root and severity of AR.

Classification

See Table 3.5.


Table 3.5 Classification of aortic regurgitation

Severity	Angiographic grade	Jet width (% of LVOT)	Regurgitant fraction (%)	ROA (cm ²)
Mild AR	Contrast enters LV, clears with systole	<25	<30	<0.1
Moderate AR	Opacification entire LV	25–65	30–49	0.1–0.29
Severe AR	Opacification LV >aorta	>65	≥50	≥0.3

Additional essential criteria: left ventricular size increased.

LVOT = left ventricular outflow tract; ROA = regurgitant orifice area.

Prognosis

Chronic AR can be well tolerated for many years and is associated with a good prognosis. 5-year survival ~75%, 10-year survival ~50%. Prognosis worsens as symptoms intervene (see box,  p.172). Acute severe AR however is associated with a high mortality from LVF, and early intervention is indicated.

Natural history of AR**Asymptomatic patients with normal LV function**

Progression to symptoms/signs CCF	<6%/year
Progression to asymptomatic LV dysfunction	<3.5%/year
Sudden death	<0.2%/year

Asymptomatic patients with LV systolic dysfunction

Progression to cardiac symptoms	>25%/year
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Symptomatic patients

Mortality rate	>10%/year
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Aortic regurgitation guidelines

Management (see also Fig. 3.4)

Medical management

- Asymptomatic mild/moderate AR with normal LV—routine follow-up (every 1–2 years) with ECHO.
- Asymptomatic severe AR with normal LV—frequent (6-monthly) follow-up—or sooner if symptoms intervene. Benefit of vasodilators is debatable.
- Severe AR with LV dysfunction or symptoms (and patient not operative candidate)—symptoms of CCF respond to loop diuretics and digoxin while arrangements are made for surgery. Vasodilators (ACE-Is, calcium-channel blockers) offer good symptomatic relief and may improve haemodynamic profile. Anginal chest pain can be treated with nitrates but use β -blockers with caution. Concomitant hypertension can worsen AR, therefore treat in the usual manner.
- Acute severe AR—urgent surgical intervention recommended. Nitroprusside and inotropic agents (dopamine, dobutamine) augment forward CO and reduce LVEDP and are useful to manage the patient temporarily before surgery. Intra-aortic balloon pump (IABP) contraindicated. Use β -blockers cautiously because they block compensatory tachycardia.

Surgical treatment

- Because of the relatively benign nature of asymptomatic AR with normal LV function, these patients should be kept under observation. Once symptoms intervene or evidence of significant LV dysfunction appears, referral for AVR/root replacement should be considered. In borderline cases frequent (2–4-monthly) follow-up is indicated.
- AVR is indicated for patients with symptomatic severe AR, or asymptomatic severe AR and $EF \leq 50\%$, severe LV dilatation (LV end-diastolic dimension >75 mm or LV end-systolic dimension >55 mm), or concomitant CABG, valvular, or aortic surgery.
- AVR is a safe effective procedure (surgical mortality 1%, complication rate thereafter 1%/year cumulative in large-volume centres, but national registries report mortality around 3%. Root replacement, performed if aortic root is dilated, is a more complex procedure, with mortality 3–5%.
- Bioprosthetic valves are preferred in older patients as they have excellent freedom from structural valve degeneration, and may be used in younger patients who want to avoid the 2–4% linearized annual risk of thromboembolic or haemorrhagic stroke.
- Valve-sparing procedures may be useful in young patients with normal leaflets where aortic AI is due to aortic root dilatation: durability may be better than bioprosthetic valves in young patients.

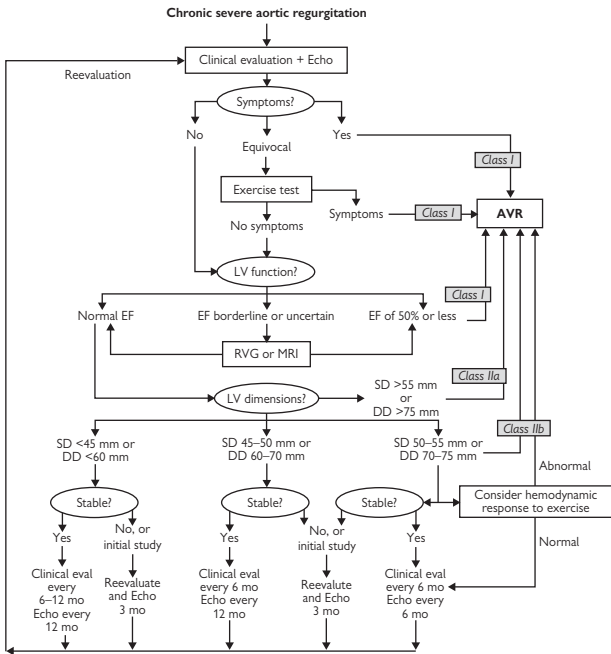


Fig. 3.4 Management strategy for patients with chronic severe aortic regurgitation. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is discordance between clinical findings and echocardiography. 'Stable' refers to stable echocardiographic measurements. In some centres, serial follow-up may be performed with radionuclide ventriculography (RVG) or magnetic resonance imaging (MRI) rather than echocardiography (Echo) to assess left ventricular (LV) volume and systolic function. AVR indicates aortic valve replacement; DD, end-diastolic dimension; EF, ejection fraction; eval, evaluation; and SD, end-systolic dimension. Reproduced with permission from *Journal of the American College of Cardiology*, Vol 48, No.3, 2006. August 1, 2006: e1-148. Bonow et al, *AHA/ACC Best Practice Guidelines*.

Tricuspid and pulmonary disease

Tricuspid regurgitation

Causes: Functional or secondary TR (normal leaflets, RV annular dilatation due to MV disease, congenital heart disease) is common. Organic tricuspid lesions: endocarditis most common (particularly intravenous (IV) drug abuse), transvalvular pacing wires, Marfan's syndrome, Ebstein anomaly, rheumatic heart disease, carcinoid.

Clinical features: Usually minimal. Peripheral oedema, ascites, nausea, anorexia, abdominal pain (tender, congested liver) are late signs.

Physical examination: Cachexia/wasting, jaundice, oedema, AF common, elevated JVP with systolic CV waves, tender pulsatile hepatomegaly. Auscultation—RV S₃ often heard (↑ in inspiration), presystolic murmur (PSM) audible at left sternal edge (LSE) (↑ in inspiration). Murmur loudest in TR secondary to pulmonary hypertension.

Investigations: ECG—non-specific, may show evidence of underlying condition. CXR—cardiomegaly in patients with functional TR, occasionally distended azygos vein, pleural effusion. TTE—colour Doppler confirms diagnosis. CW Doppler of TR jet can assess PA systolic pressure. Two-dimensional (2D) images can give idea of cause of TR (RV infarction, ventricular septal defect (VSD), Ebstein, etc.) Severe TR—jet width >0.7 cm and systolic flow reversal in hepatic veins.

Treatment

- In the absence of pulmonary hypertension, TR is well tolerated and may not require specific treatment (indeed in SBE of TV, valve excision is sometimes performed with good recovery).
- Symptoms of RV failure respond to diuretics and fluid/salt restriction.
- If co-existent MV disease is being operated on and TR is mild (with normal PA pressure), TR may improve postoperatively as PA pressure falls.
- TV annuloplasty is indicated in patients undergoing MVR with severe or moderate TR and annular dilatation or pulmonary hypertension.
- TR secondary to valve pathology (Ebstein, carcinoid) may require valve replacement, preferably with a large bioprosthesis to minimize the risk of thrombosis (but high operative mortality ~15%).

Tricuspid stenosis

Causes: Rheumatic heart disease (almost always associated with MS), congenital, carcinoid, pacemaker lead. Extremely rare.

Clinical features: Fatigue, anorexia, peripheral oedema.

Physical examination: Wasting, oedema, hepatomegaly, ↑JVP, prominent 'a' waves, rumbling mid-diastolic murmur at LLSE in inspiration.

Investigations: ECG—sinus rhythm with signs RA enlargement (↑'P' waves in II, V¹—often coincides with signs of LA enlargement because of MS) but no RVH. CXR—enlarged RA but normal PA size. TTE—2D image can show thickened restricted leaflets. CW Doppler is diagnostic. Severe TS—valve area <1.0 cm². Look for co-existent MS.

Management: Salt restriction and diuretics. If co-existent MS is being operated on then surgical valvuloplasty may help. TV replacement is occasionally performed. Bioprosthetic valves give better results than mechanical valves. There is recent evidence of usefulness of TV balloon valvuloplasty but use remains controversial.

Pulmonic stenosis

Causes: Congenital (virtually all), carcinoid, rheumatic, compression.

Clinical features: Usually none. If longstanding severe stenosis—exertional dyspnoea, light-headedness/syncope (inability to \uparrow CO). Ultimately may develop TR symptoms of RV failure (see previous).

Physical examination: Prominent 'a' wave in JVP, RV heave, occasionally thrill in 2nd left intercostal space. Auscultation—widely split S_2 (as pulmonary valve (PV) closure becomes later), P_2 becomes softer (unless stenosis is supra-valvular), ejection systolic murmur (ESM) at left edge of upper sternum, heard best in inspiration.

Investigations: ECG—RVH and RA enlargement. CXR—dilated pulmonary arteries, occasionally with calcification of valve, if severe then oligoemic lung fields. TTE—confirms diagnosis and can show level of stenosis (valvular, supra-valvular or RV outflow tract) and severity. Severe pulmonic stenosis (PS): jet velocity >4 m/s or max gradient >60 mmHg. Will also show associated conditions (ASD, patent ductus arteriosus (PDA), Fallot's, etc). Cardiac catheterization—to assess severity of obstruction and haemodynamic effects.

Management: In general, invasive intervention is recommended when gradient across valve is >40 mmHg at rest or when symptoms occur. Medical—supportive/symptomatic treatment of RV failure, diuretics, fluid restriction (cautious). Balloon valvuloplasty—treatment of choice for stenosis at valvular level. Highly effective, safe with good long-term results. Pulmonary regurgitation (PR) is common following valvuloplasty, but is rarely clinically important. Surgical—valvotomy is very effective with minimal recurrence. Pulmonic valve replacement—indicated if not suitable for above treatments or for severe PR following these treatments.

Pulmonary regurgitation

Causes: Any cause of pulmonary hypertension (causes dilatation of valve ring), infective endocarditis, connective tissue disease (e.g. Marfan's), iatrogenic (following valvotomy or PA catheter placement), carcinoid.

Clinical features: Often asymptomatic. Symptoms occur when pulmonary hypertension or RV failure exist. Then patients get dyspnoea on exertion, lethargy, peripheral oedema, abdominal pain.

Physical examination: RV heave, occasionally a thrill in pulmonary area. Auscultation— P_2 may be delayed (large SV), loud (if pulmonary \uparrow BP), or soft (if PV stenosis). Murmur of PR heard best in 3rd/4th intercostal space on left adjacent to sternum, I during inspiration.

Investigations: ECG—RVH (if pulmonary \uparrow BP), right bundle branch block (RBBB)/rsR pattern in V₁. CXR—enlarged PA and RV. TTE—2D images may show RV dilatation/hypertrophy. Abnormal septal motion if RV volume overload. PR seen on colour Doppler and quantified with pulsed Doppler. Severe PR—colour jet fills outflow tract.

Management: Usually supportive treatment suffices. Treat RV failure in usual way (diuretics, etc). If PR is due to PV ring dilatation secondary to pulmonary hypertension, treating the underlying cause of pulmonary \uparrow BP can decrease the severity of PR (e.g. mitral valve surgery). If there is symptomatic right heart failure with severe PR, then PV replacement should be considered. Indications for PVR in asymptomatic individuals remain unclear.

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Prosthetic heart valves

Types

See Fig. 3.5.

Mechanical: Bileaflet (St Jude Medical[®], Carbomedics[®]) most common today. Ball and cage (Starr–Edwards[®]) or tilting disc (Medtronic Hall[®])

Bioprosthetic: Porcine (stented or stentless) or bovine pericardium (Carpentier–Edwards)

Non prosthetic valves: Homograft (preserved cadaveric human valve), autograft (pulmonary valve—Ross procedure)

Mechanical valves

Minimal risk of structural failure. Lifetime risk of reoperation for non-structural valve dysfunction around 5%. Thrombogenic, therefore requiring lifelong warfarin therapy (\pm aspirin if high risk). Even with optimal INR, there is 2–4% linearized annual lifetime risk of major thromboembolic or haemorrhagic events, including stroke.

Tissue valves

(Bioprosthetic or homograft) do not require anticoagulation but are not as durable as mechanical valves (15-year failure rate of 5–20% for bioprostheses depending on patient age—best durability in older patients). 0.5% linearized annual risk of thromboembolism. More likely to have post-operative gradient than mechanical valves in smaller sizes.

Valve haemodynamics

Different prosthetic valves have unique profiles and effective orifice area. For any given valve dimension, bioprosthetic valves have the smallest effective orifice area and bileaflet valves the best.

Assessment of prosthetic valve function

Clinically: Each prosthetic valve produces a distinctive sound. Dysfunction may be indicated by new sounds, a change in sound or volume of sound, or a new (or changing) murmur.

Imaging modality: *Fluoroscopy* can be used to assess valve leaflet movement (in mechanical valves). Diminished motion in thrombosis, excessive movement of base ring if valve dehisced. *TTE*—limited use because of ECHO shadow caused by metal in valve. Can be used to look at valve ring motion (in mechanical valves), leaflet motion (in tissue valves), and regurgitation (with Doppler). *TOE*—better at assessing prosthetic mitral valve function but less good at prosthetic aortic valve assessment. *Magnetic resonance imaging (MRI)*—safe in majority of modern mechanical valves. Expensive and time consuming, therefore reserved for cases when TTE/TOE is inconclusive.

Cardiac catheterization: Can assess valve gradient (and therefore valve area). Can quantify degree of regurgitation. Risk of passing catheter across mechanical valves; therefore used prior to reoperation or when non-invasive tests are inconclusive.

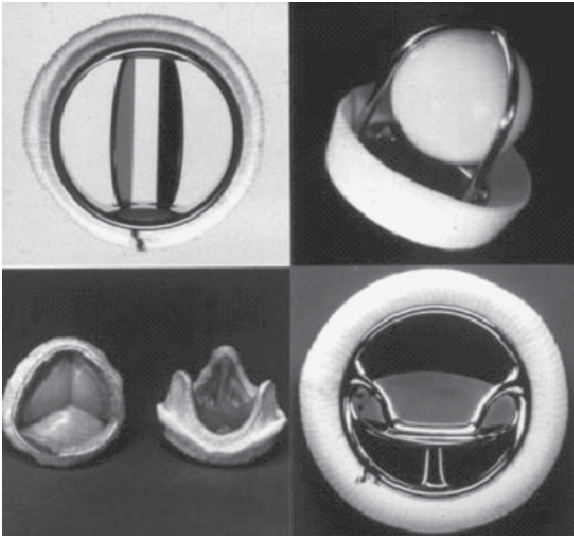


Fig. 3.5 Common types of heart valve prostheses (from top left clockwise): St Jude's Medical[®] bileaflet, Starr-Edwards[®] ball and cage, Bjork-Shiley[®] tilting disk, stented porcine prosthesis. Reproduced with permission from Bloomfield P (2002). *Heart* **87**: 583–9.

Choice of the prosthesis: in favour of mechanical prosthesis^a

- Desire of the informed patient and absence of contraindication for long-term anticoagulation
- Patients at risk of accelerated structural valve deterioration^b
- Patients already on anticoagulation because of other mechanical prosthesis
- Patients already on anticoagulation because at high risk for thromboembolism^c
- Age <65–70 years and long life expectancy^d
- Patients for whom future redo valve surgery would be at high risk (due to LV dysfunction, previous CABG, multiple valve prosthesis).

^a The decision is based on the integration of several of the factors given in the table.

^b Young age, hyperparathyroidism.

^c Risk factors for thromboembolism: severe LV dysfunction, atrial fibrillation, previous thromboembolism, hypercoagulable state.

^d According to age, sex, the presence of co-morbidity, and country-specific life expectancy.


Adapted from European Society of Cardiology (ESC) (2007). Guidelines on the Management of Valvular Heart Disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* **28**: 230–68. <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-VHD-FT.pdf>

Choice of the prosthesis: in favour of bioprosthesis^a

- Desire of the informed patient
- Unavailability of good-quality anticoagulation (contraindication or high risk, unwillingness, compliance problems, lifestyle, occupation)
- Reoperation for mechanical valve thrombosis in a patient with proven poor anticoagulant control
- Patient for whom future redo valve surgery would be at low risk
- Limited life expectancy^b, severe co-morbidity, or age >65–70 years
- Young woman contemplating pregnancy.

^a The decision is based on the integration of several of the factors given in the table.

^b According to age, sex, the presence of co-morbidity, and country-specific life expectancy.

Adapted from European Society of Cardiology (ESC) (2007). Guidelines on the Management of Valvular Heart Disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* **28**: 230–68.  <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-VHD-FT.pdf>.

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Prosthetic valve complications

Valve thrombosis

Incidence: 0.1–5.7% per patient-year; <0.01% per day if anticoagulation withheld (may be necessary for life-threatening bleed).

Risks: Inadequate anticoagulation and mitral prostheses. Ball and cage valve at lower risk as occluder travels completely out of housing. Bileaflet valve can continue to work partially, but single leaflet may fail catastrophically.

Clinical presentation: Pulmonary oedema, embolization, sudden death.

Investigation: ↓intensity of valve sounds, ↓movement of leaflets on TTE or fluoroscopy (and ↑valve gradient on TTE).

Treatment: Anticoagulation with heparin. If thrombus is <5 mm on TTE, then anticoagulation may suffice. If >5 mm then will need further treatment (thrombolysis, thrombectomy or valve replacement). High recurrence rate if valve not replaced.

Prognosis: Valve replacement for valve thrombus has mortality rate of <15%, thrombolysis has mortality rate of <10% (with embolization in <20%). Thrombolysis may be more effective for aortic valve thrombosis and in recent (<2 week) onset.

Embolization

Most manifest as cerebral infarctions.

Incidence: In unanticoagulated patients ~5% per patient-year (causing death or stroke), 1–2% per patient-year on therapeutic anticoagulation

Risks: AF, age >70 years, ↓LV function, mitral prostheses, ball and cage valves, >1 valve. Consider endocarditis in patients with prosthetic valves presenting with peripheral embolization. If cerebral embolization, perform immediate computed tomography (CT) to exclude bleed (if bleed confirmed, withhold anticoagulation and seek specialist help).

Haemolysis

A low level of background haemolysis is common in patients with mechanical prostheses (even when functioning normally). Severe haemolysis is uncommon and is usually secondary to valve dysfunction (leakage, dehiscence, infection).

Investigation: ↓ haemoglobin (Hb), ↑ lactate dehydrogenase (LDH), ↓serum haptoglobin level, reticulocytosis.

Treatment: Treat underlying problem (including further valve surgery), blood transfusion, folic acid, ferrous sulphate. Occasionally re-replacement is required for cases requiring frequent blood transfusion.

Endocarditis (see  Coronary artery disease, Chapter 5, p. 211)

Prevalence: Lifetime risk around 3–6% of patients with prosthetic valves. Early endocarditis cases occur within 60 days of valve surgery, and late endocarditis occurs >60 days since surgery. Early prosthetic valve

endocarditis (PVE) usually arises from skin/wound infections or from indwelling IV cannulae. Commonly due to *S. aureus*, *S. epidermidis*, Gram-negative bacteria, and fungi. Late PVE has similar organisms as native valve endocarditis (mainly streptococci). Similar risk for tissue and mechanical valves.

Structural valve degeneration and reoperation

Incidence: Structural valve degeneration (SVD) is inevitable for all currently available bioprosthetic valves if the patient lives long enough. Valves calcify, leaflets tear, resulting in regurgitation \pm stenosis.

- Freedom from SVD \approx 90% at 12 years, for AVR in 60 year old, decreasing rapidly beyond 15 years of follow-up.
- Freedom from reoperation for 2nd-generation bioprostheses $>$ 90% at 10 years, \approx 70% at 15 years (worse in younger patients, mitral position).
- Freedom from reoperation (for pannus, endocarditis, thrombosis) for mechanical valves $>$ 95% at 10 years and approximately 90% at 10 years.

Risks: Earlier-generation valves, young age, mitral position, renal failure (because of the greater pressure differential across the closed mitral valve in systole, compared to the closed aortic valve in diastole):

- no clear evidence that porcine $>$ bovine, stented $>$ stentless, homografts $>$ xenografts
- although renal failure predisposes to accelerated calcification, there is no increase in reoperation, because of lower life expectancy.

Investigation: Clinical and TTE findings of regurgitation or stenosis.

Treatment: As for primary valve lesion, although closer follow-up is required as prosthetic valve function can deteriorate more quickly: reoperation poses 1–5% extra risk of mortality/morbidity above first-time surgery.

Patient-prosthesis mismatch

AVR 'too small' for patient: defined as:

- effective orifice area (EOA) is less than that of a normal human valve
- ERO indexed to body surface area (BSA) $<$ 0.85 cm²/m² (normal indexed EOA $<$ 2.0 \pm 0.3 cm²/m²).
- A 21 mm Carpentier–Edwards Perimount valve has an EOA of 1.2 cm², and would provide an indexed EOA of $<$ 0.8 cm²/m² if inserted into a patient with BSA $>$ 1.6 m².
- Severe patient-prosthesis mismatch (PPM) is EOA $<$ 0.65cm²/m².

Incidence: Severe PPM \approx 2–11% of postoperative AVR. Stented valves in smaller sizes are partially stenotic, and mild to moderate transvalvular aortic gradients are not uncommon in the immediate postoperative period. The data regarding the clinical relevance of patient prosthesis mismatch are conflicting: definitions of mismatch, baseline patient characteristics, and end-points vary widely between studies. Several studies link PPM with decreased postoperative cardiac index and New York Heart Association (NYHA) functional class, and reduced LV mass regression, poorer survival, and late adverse events.

Paravalvular leak

Incidence: 0–1.5% per patient-year.

Risk: St Jude Silzone® valves, thinner sewing rings, calcified annulus, incomplete debridement of calcium/previous sutures, active endocarditis.

Late paravalvular leaks are suggestive of prosthetic valve endocarditis. Paravalvular leaks generally result in haemolysis that is more severe than that associated with older, normally functioning, prosthetic valves.

Investigation: TTE, endocarditis work-up, screen for haemolysis.

Treatment: Severe haemolysis, insufficiency, valve dehiscence, evidence of endocarditis are surgical indications, otherwise frequent TTE follow-up.

Infective endocarditis

- Presentation of endocarditis 188
- Diagnosis of endocarditis 190
- Investigation of endocarditis 192
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- Culture-negative endocarditis 198
- Prosthetic valve endocarditis 200
- Surgery for endocarditis 202
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- Outpatient review 208

Presentation of endocarditis

Key facts

- Highly variable presentation—depends on intracardiac pathology, virulence of organism, and extracardiac involvement.
- Presentation can be insidious, as in streptococcal infections, or with striking constitutional symptoms as in *Staphylococcus aureus* infection. Presenting features can include those discussed next.

General manifestations of sepsis

Includes malaise, anorexia, weight loss, fever, rigors, and night sweats. Longstanding infection produces anaemia, clubbing, and splenomegaly.

Cardiac manifestations of endocarditis

- Sepsis causing tachycardia, hypotension.
- Valve destruction results in a new or changing murmur. This may result in progressive heart failure and pulmonary oedema.
- A new harsh pansystolic murmur and acute deterioration may be due to perforation of the interventricular septum or rupture of a sinus of Valsalva aneurysm into the right ventricle.
- High-degree atrioventricular (AV) block (2–4% of infective endocarditis (IE)) occurs with intracardiac extension of infection into the interventricular septum (e.g. from aortic valve).
- Intracardiac abscess may be seen with any valve infection (25–50% of aortic endocarditis, 1–5% of mitral but rarely with tricuspid) and is most common in prosthetic valve endocarditis.
- Pericarditis.

Manifestations of immune complex deposition

Skin: Petechiae (most common), splinter haemorrhages; Osler's nodes (small tender nodules (pulp infarcts) on hands and feet and persist hours to days); Janeway lesions (non-tender erythematous and/or haemorrhagic areas on the palms and soles).

Eye: Roth spots (oval retinal haemorrhages with a pale centre located near the optic disc), conjunctival splinter haemorrhages, retinal flame haemorrhages.

Renal: Microscopic haematuria, glomerulonephritis and renal impairment.

Cerebral: Toxic encephalopathy.


Musculoskeletal: Arthralgia or arthritis.

Systemic manifestations of endocarditis

General manifestations of sepsis

Includes malaise, anorexia, weight loss, fever, rigors, and night sweats. Longstanding infection produces anaemia, clubbing, and splenomegaly.

Septic emboli

- Septic emboli are seen in 20–45% of patients and may involve any circulation (brain, limbs, coronary, kidney, or spleen; pulmonary emboli with tricuspid endocarditis (see  Right-sided endocarditis, p. 190).
- ~40% of patients who have had an embolic event will have another.
- The risk depends on the organism (most common with Gram-negative infections, *S. aureus* or *candida*) and the presence and size of vegetations

(emboli in 30% of patients with no vegetation on echocardiography, 40% with vegetations <5 mm and 65% with vegetations >5 mm).

- Ask specifically for a history of dental work, infections, surgery, intravenous (IV) drug use, or instrumentation, which may have led to a bacteraemia.
- Examine for any potential sources of infection, e.g. teeth/skin lesions.
- Risk factors for endocarditis are shown in the box below.

Risk factors for infective endocarditis

High risk	Prosthetic valves Previous bacterial endocarditis Aortic valve disease Mitral regurgitation or mixed mitral disease Cyanotic congenital heart disease Patent ductus arteriosus Uncorrected L→R shunt Intracardiac and systemic-pulmonary shunts
Moderate risk	Mitral valve prolapse (MVP) with regurgitation or valve thickening Isolated mitral stenosis Tricuspid valve disease Pulmonary stenosis Hypertrophic cardiomyopathy Bicuspid aortic valve disease Degenerative valve disease in elderly Mural thrombus (e.g. post infarction)
Low risk	MVP without regurgitation Tricuspid incompetence without structural abnormality Isolated atrial septal defect (ASD) Surgically corrected L→R shunt with no residual shunt Calcification of mitral valve (MV) annulus Ischaemic heart disease and/or previous coronary artery bypass graft (CABG) Permanent pacemaker Atrial myxoma

Other predisposing factors

- Arterial prostheses or arteriovenous fistulae
- Recurrent bacteraemia, e.g. IV drug users, severe periodontal disease, colon carcinoma)
- Conditions predisposing to infections, e.g. diabetes, renal failure, alcoholism, immunosuppression)
- Recent central line.

In many cases no obvious risk factor is identified.

Diagnosis of endocarditis

Key facts

- Clinical features can be non-specific and diagnosis difficult.
- Maintain a high index of suspicion in patients presenting with unexplained fever, a predisposing cardiac lesion, bacteraemia, and embolic phenomena.

Duke classification

- Developed in 1994 as a means of standardizing the diagnosis of IE
- Highly specific (99%) and sensitive (92%)
- Several modifications, the most current version is described next.

Major criteria

- *Positive blood culture*
 - Typical microorganism for IE from two separate blood cultures¹
 - Persistently positive blood culture²
 - Single positive blood culture for *Coxiella Burnetii* or phase I antibody
 - Titre to *C. Burnetii* >1:800
- *Evidence of endocardial involvement*: positive echocardiogram
 - oscillating intracardiac mass (vegetation)
 - abscess
 - new partial dehiscence of prosthetic valve
 - new valve regurgitation.

Minor criteria

- Predisposing condition or drug use
- Fever >38°C
- *Vascular phenomena*: arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial and conjunctival haemorrhage, Janeway lesions
- *Immunologic phenomena*: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- *Microbiological evidence*: positive blood cultures but not meeting major criteria or serological evidence of organism consistent with IE
- *Echocardiogram*: positive for IE but not meeting major criteria
- Always consider this diagnosis in IV drug users (or patients with venous access).
- Endocarditis on endocardial permanent pacemaker leads is a rare but recognized cause.

Right-sided endocarditis

- Patients most commonly have staphylococcal infection and are unwell, requiring immediate treatment and often early surgery.
- Lesions may be sterilized with IV antibiotics.

¹ Strep viridans, strep bovis, HACEK group (HACEK = *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* spp.), community-acquired *Staphylococcus aureus*, or enterococci in the absence of primary focus.

² Blood cultures drawn 12 hours apart or 3 or more cultures with the first and last drawn 1 hour apart.

- Surgery may be required for:
 - resistant organisms (*Staphylococcus aureus*, *Pseudomonas*, *Candida* and infection with multiple organisms).
 - increasing vegetation size in spite of therapy.
 - infections on pacemaker leads (surgical removal of lead and repair or excision of tricuspid valve).
 - recurrent mycotic emboli.

Criteria for definite diagnosis

- *Definite endocarditis*: 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria
- *Possible endocarditis*: findings that fall short of definite endocarditis but are not rejected
- *Rejected diagnosis*: firm alternative diagnosis, or sustained resolution of clinical features with <4 days of antibiotic therapy

Common organisms in IE

50–60%	Streptococci (esp. <i>Strep. viridans</i> group)
10%	Enterococci
25%	Staphylococci
	<i>S. aureus</i> = coagulase +ve
	<i>S. epidermidis</i> = coagulase –ve
5–10%	Culture negative
<1%	Gram-negative bacilli
<1%	Multiple organisms
<1%	Diphtheroids
<1%	Fungi

Investigation of endocarditis

● Blood cultures	Take 3–4 sets of cultures from different sites at least an hour apart and inoculate a minimum of 10 mL/bottle for the optimal pick-up rate. Both aerobic and anaerobic bottles must be used. Lab should be advised that IE is a possibility, especially if unusual organisms are suspected. In stable patients on antibiotic therapy, doses must be delayed to allow culture on successive days. Ask for prolonged (fungal) cultures in IV drug users.
● Full blood count (FBC)	May show normochromic, normocytic anaemia (exclude haematinic deficiency), neutrophil leucocytosis, and perhaps thrombocytopenia.
● Urea and electrolytes (U&Es)	May be deranged (this should be monitored throughout treatment).
● Liver function tests (LFTs)	May be deranged, especially with an increase in alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT).
● Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)	Acute phase reaction.
● Urinalysis	Microscopic haematuria ± proteinuria.
● Immunology	Polyclonal elevation in serum Igs, complement levels
● Electrocardiogram (ECG)	May have changes associated with any underlying cause. There may be atrioventricular (AV) block or conduction defects (especially aortic root abscess) and, rarely (embolic), acute myocardial infarction (MI).
● Chest X-ray (CXR)	May be normal. Look for pulmonary oedema or multiple infected or infarcted areas from septic emboli (tricuspid endocarditis).

● Echocardiography (ECHO)	Transthoracic ECHO may confirm the presence of valve lesions and/or demonstrate vegetations if >2 mm in size. Transoesophageal echocardiography (TOE) is more sensitive for aortic root abscess and mitral leaflet involvement. A normal ECHO does not exclude the diagnosis.
● Magnetic resonance imaging (MRI, used rarely)	Useful in investigation of paravalvular extension, aortic root aneurysm, and fistulas.
● Dentition	All patients should have an OPG (orthopantomogram—a panoramic dental X-ray) and a dental opinion.
● Swabs	Any potential sites of infection (skin lesions).
● Ventilation/perfusion (V/Q) scan	In cases where right-sided endocarditis is suspected, this may show multiple mismatched defects.
● Save serum for:	<i>Aspergillus precipitins</i> ; <i>Candida</i> antibodies (rise in titre); Q fever (<i>Coxiella burnetti</i>) complement fixation test; <i>Chlamydia</i> complement fixation test; <i>Brucella</i> agglutinins; <i>Legionella</i> antibodies; <i>Bartonella</i> species.

Further reading

Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis (new version 2009), The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* 30: 2369–413. <http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/infective-endocarditis.aspx>

Antibiotics in endocarditis

Key facts

- Be guided by your local microbiologist and always follow local antibiotic prescription guidelines.
- Once diagnosis is confirmed (or even suspected), explain to the patient the need for a prolonged parenteral (usually IV) course of antibiotics.
- Microbiology will determine sensitivities to, and minimum inhibitory concentration (MIC) of, appropriate antibiotics—if fully sensitive organism with 'low' MIC then shorter courses of antibiotics may suffice (and the latter part of the course may be completed on an outpatient basis). Evidence shows that combination therapy is more effective than single chemotherapeutic agents.
- Identification of an organism is invaluable for further management, and blood cultures should be taken before antibiotics, with meticulous attention to detail.

Specific antibiotic therapy

Streptococcus viridans group

- Fully sensitive (MIC of penicillin <0.1 mg/L)—native valve endocarditis (NVE): benzylpenicillin 1.2 g/4 h IV for 4 weeks, occasionally can successfully treat with 2-week course of benzylpenicillin and gentamicin. For prosthetic valve endocarditis (PVE): benzylpenicillin for 6 weeks (in combination with gentamicin for first 2 weeks).
- Mild penicillin resistance (MIC of penicillin >0.1 – 0.5 mg/L)—NVE: benzylpenicillin for 4 weeks with gentamicin for first 2 weeks. PVE: benzylpenicillin for 6 weeks with gentamicin for first 4 weeks.
- Moderate penicillin resistance (MIC >0.5 mg/L)—NVE: benzylpenicillin (or amoxicillin) and gentamicin for 4–6 weeks. PVE: benzylpenicillin (or amoxicillin) and gentamicin for at least 6 weeks.
- NB: can use vancomycin if allergic to penicillin.

Staphylococcus species

- Meticillin-sensitive staphylococci—NVE: flucloxacillin 2 g/6 hours IV for 4–6 weeks with gentamicin for at least 1st week. PVE: flucloxacillin for 6 weeks + gentamicin for first 2 weeks + rifampicin 600 mg bd PO for 6 weeks.
- Meticillin-resistant staphylococci—NVE: IV vancomycin for 4–6 weeks \pm gentamicin for 1st week. PVE: vancomycin + rifampicin for 6 weeks + gentamicin for 2 weeks.

Enterococcus species

- As for streptococcus with moderate penicillin resistance (above).

HACEK species

- NVE: IV cephalosporin (e.g. ceftriaxone) for 4 weeks, or 6 weeks for PVE.

***Coxiella burnetii* (Q fever)**

- NVE and PVE: requires prolonged (3–4 years) therapy with tetracycline (e.g. doxycycline) and second agent (co-trimoxazole, rifampicin, quinolone) with careful monitoring of immunoglobulin G (IgG) titres. Usually requires surgery.

Empirical therapy

- Infective endocarditis is usually a clinical diagnosis and must be considered in any patient with a typical history, fever, and a murmur with no other explanation. Often antibiotics need to be started before the culture results are available. Be guided by the clinical setting (see Table 4.1¹).

Table 4.1 Presentation of endocarditis

Presentation	Choice of antibiotic
Gradual onset (weeks)	Benzylpenicillin + gentamicin
Acute onset (days) or history of skin trauma	Flucloxacillin + gentamicin
Recent valve prosthesis (possible methicillin-resistant <i>S. aureus</i> (MRSA), diphtheroid, <i>Klebsiella</i> , corynebacterium, or nosocomial staphylococci)	Vancomycin (or teicoplanin) + gentamicin + rifampicin
IV drug user	Vancomycin

Suggested antibiotic doses



Benzylpenicillin	4 MU (2.4 g) q4h IV
Flucloxacillin	2 g qds IV
Vancomycin	15 mg/kg q12h IV over 60 min, guided by levels
Gentamicin	3 mg/kg divided in 1–3 doses guided by levels
Rifampicin	300 mg q12h po
Ciprofloxacin	400mg q12h IV for 1 week, then 750 mg q12h PO for 3 weeks

- IV antibiotics should be given via a tunnelled CVP (central venous pressure (Hickman)) line.
- Antibiotic therapy may be modified for sensitivities.
- Suggested antibiotic combinations are shown above; however, individual units may have specific policies; individual patients should be discussed with your local microbiologist.

¹ Oakley CM (1995). The medical treatment of culture-negative infective endocarditis. *Eur Heart J* 16(suppl B): 90–3.

Stopping endocarditis treatment

Duration of treatment

- Controversial—a trend toward shorter courses. Microbiology and ID opinion is important, especially in resistant and/or uncommon organisms. The box below shows one suggested protocol.
 - The duration of treatment varies depending on the severity of infection and the infecting organism. IV therapy is usually for at least 2 weeks, and total antibiotic therapy for 4–6 weeks.
 - If the patient is well following this period, antibiotic treatment may be stopped. Provided no surgery is indicated (see  Surgery for endocarditis, p. 202), the patient may be discharged and followed up in outpatient clinic.
 - Patients should be advised of the need for endocarditis prophylaxis in the future (see  Endocarditis prophylaxis, p. 206).
 - Patients with valvular damage following infection should be followed long term, and patients with ventricular septal defects should be considered for closure.
-
- Viridans streptococci and *Streptococcus bovis* (penicillin sensitive)
 - Benzylpenicillin only (4 weeks)
 - Vancomycin or teicoplanin (4 weeks)
 - Penicillin + aminoglycoside (2 weeks)
 - Ceftriaxone 2 g (4 weeks)
 - Group B, C, G streptococci, *Strep. pyogenes*, *Strep. pneumoniae*
 - Penicillin (4 weeks) + aminoglycoside (2 weeks)
 - Vancomycin (4 weeks) + aminoglycoside (2 weeks)
 - Group A streptococci
 - Penicillin (4 weeks)
 - Vancomycin (4 weeks)
 - Enterococci
 - Penicillin + aminoglycoside (4–6 weeks)
 - Vancomycin + aminoglycoside (4–6 weeks)
 - Extracardiac infection from septic emboli
 - Penicillin (4 weeks) + aminoglycoside (2 weeks)
 - Vancomycin (4 weeks) + aminoglycoside (2 weeks)
 - *Staphylococcus aureus* and coagulase-negative staphylococci
 - Left-sided endocarditis:
 - Flucloxacillin (4–6 weeks) + aminoglycoside (2 weeks)
 - If MRSA—vancomycin + rifampicin (6 weeks) ± aminoglycoside (2 weeks)
 - Right-sided endocarditis:
 - Flucloxacillin (2 weeks) + aminoglycoside (2 weeks)
 - Ciprofloxacin (4 weeks) + rifampicin (3 weeks)
 - If MRSA—vancomycin (4 weeks) + rifampicin (4 weeks)
 - Fungi
 - Amphotericin B IV to a total dose of 2.5–3 g


Monitoring treatment

Patients need careful clinical monitoring both during and for several months after the infection. Reappearance of features suggestive of IE must be investigated thoroughly to rule out recurrent infection or resistance to the treatment regime.

Clinical features of progressive endocarditis

- Signs of continued infection, persistent pyrexia, and the persistence of systemic symptoms
- Persistent fever may be due to drug resistance, concomitant infection (central line, urine, chest, septic emboli to lungs or abdomen), or allergy (?eosinophilia, ?leucopenia, ?proteinuria: common with penicillin but may be due to any antibiotic—consider changing or stopping antibiotics for 2–3 days)
- Changes in any cardiac murmurs or signs of cardiac failure
- The development of any new embolic phenomena
- Inspect venous access sites daily. Change peripheral cannulae every 3–4 days.

Echocardiography

- Regular (weekly) transthoracic echocardiograms may identify clinically silent, but progressive, valve destruction and development of intracardiac abscesses or vegetations.
- The tips of longstanding central lines may develop sterile fibrinous 'fronds', which may be visible on TOE: change the line and send the tip for culture.
- 'Vegetations' need not be due to infection (see  Causes of 'vegetations' on ECHO, Culture-negative endocarditis, p. 199).

ECG

- Look specifically for AV block or conduction abnormalities suggesting intracardiac extension of the infection. A daily ECG must be performed.


Microbiology

- Repeated blood cultures (especially if there is continued fever)
- Regular aminoglycoside and vancomycin levels (ensuring the absence of toxic levels and the presence of therapeutic levels). Gentamicin ototoxicity may develop with prolonged use even in the absence of toxic levels
- Back titration to ensure that minimum inhibitory and bactericidal concentrations are being achieved.

Laboratory indices

- Regular (daily) urinalysis
- Regular U&Es and LFTs
- Regular CRP (ESR every 2 weeks)
- FBC—rising haemoglobin (Hb) and falling white cell count (WCC) suggests successful treatment; watch for beta-lactam-associated neutropenia
- Serum magnesium (if on gentamicin).

Culture-negative endocarditis

- The commonest reason for persistently negative blood cultures is prior antibiotic therapy and affects up to 15% of patients with diagnosis of IE.
- If the clinical response to the antibiotics is good, these should be continued.
- For a persisting fever:
 - withhold antibiotics if not already started
 - consider other investigations for a 'PUO' (pyrexia of unknown origin)
 - if there the clinical suspicion of IE is high, it warrants further investigation
 - repeated physical examination for any new signs
 - regular ECHO and TOE. 'Vegetations' need not be due to infection (see  p.199)
 - repeated blood cultures, especially when the temperature is raised. Discuss with microbiology about prolonged culturing times (4+ weeks) and special culturing and subculturing techniques. Most HACEK group organisms can be detected
- Consider unusual causes of endocarditis:
 - *Q-fever (Coxiella burnetii)*: complement fixation tests identify antibodies to phase 1 and 2 antigens. Phase 2 antigens are raised in the acute illness; phase 1 antigens are raised in chronic illnesses such as endocarditis. Polymerase chain reaction (PCR) can be performed on operative specimens. Treat with indefinite (lifelong) oral doxycycline ± co-trimoxazole, rifampicin, or quinolone
 - *Chlamydia psittaci*: commonly there is a history of exposure to birds and there may be an associated atypical pneumonia. Diagnosis is confirmed using complement fixation tests to detect raised antibody titres
 - *brucellosis*: blood cultures may be positive, though organisms may take up to 8 weeks to grow. Serology usually confirms the diagnosis
 - *fungi*: *Candida* is the most common species and may be cultured. The detection of antibodies may be helpful, though levels may be raised in normal individuals. The detection of a rising titre is of more use. Other fungal infections (e.g. histoplasmosis, aspergillosis) are rare, but may be diagnosed with culture or serology, though these are commonly negative. Antigen assays may be positive, or the organism may be isolated from biopsy material. Fungal IE is more common in patients with prosthetic valves, and IV drug users. Bulky vegetations are common. Treatment is with amphotericin B ± flucytosine. Prosthetic valves must be removed. Mortality is >50%.

Causes of culture-negative endocarditis

- Previous antibiotic therapy
- Fastidious organism:
 - nutritionally deficient variants of *Strep. viridans*
 - *Brucella*, *Neisseria*, *Legionella*, *Nocardia*
 - Mycobacteria
 - The HACEK group of oropharyngeal flora
 - Cell-wall-deficient bacteria and anaerobes
- Cell-dependent organism:
 - *Chlamydia*, rickettsiae (*Coxiella*)
- Fungi

Causes of 'vegetations' on ECHO

- Infective endocarditis
- Sterile thrombotic vegetations:
 - Libman-Sacks endocarditis (SLE)
 - primary anti-phospholipid syndrome
 - marantic endocarditis (adenocarcinoma)
- Myxomatous degeneration of valve (commonly mitral)
- Ruptured mitral chordae
- Exuberant rheumatic vegetations (Black Africans)
- Thrombus ('pannus') on a prosthetic valve
- A stitch or residual calcium after valve replacement

SLE = systemic lupus erythematosus.

Prosthetic valve endocarditis

Key facts

- Devastating complication—frequently needs reoperative surgery
- Conventionally divided into early (<2 months postoperatively) and late (>2 months postoperatively).

Early prosthetic valve endocarditis

Incidence <1%

Causes: Most commonly due to staphylococci, Gram-negative bacilli, diphtheroids, or fungi. Generally infection has begun either preoperatively or in the immediate postoperative period

Risks: Prior endocarditis, prolonged hospital stay

Clinical features: Often a highly destructive, fulminant infection with paravalvular leak, valve dehiscence, abscess formation, and rapid haemodynamic deterioration

Treatment: Discuss with the surgeons early. Patients commonly require reoperation. Mortality is high (45–75%)

Late prosthetic valve endocarditis


Causes: The pathogenesis is different—two mechanisms:

- abnormal flow around the prosthetic valve ring produces micro thrombi and non-bacterial thrombotic vegetations (NBTV), which may be infected during transient bacteraemia. The source is commonly dental or urological sepsis, or from indwelling venous lines
- early infection with indolent organism (e.g. *Strep. epidermidis*) that takes several months to manifest clinically.

Common organisms are coagulase-negative staphylococci, *Staph. aureus*, *Strep. viridans*, or enterococci.

Risks: Invasive procedures, dental sepsis—as for primary endocarditis.

Treatment: Frequently needs surgical intervention and this carries a high mortality, but less than for early PVE.

It may be possible to sterilize infections on bioprostheses with IV antibiotics only. Surgery (see  Surgery for endocarditis, p. 202) may then be deferred.

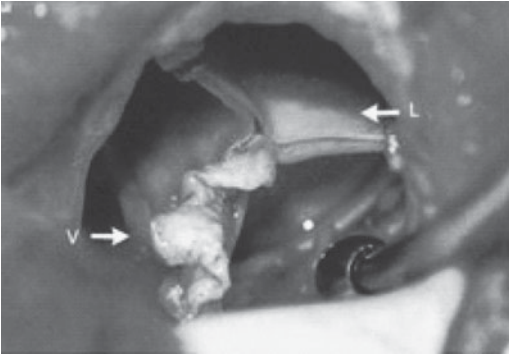


Fig. 4.1 Mobile vegetation (V) attached to the leaflet (L) of a prosthetic aortic valve in a man with infective endocarditis. Reproduced with permission from Tuna IÇ, Harrison MR (2001). Images in clinical medicine. *N Engl J Med* **344**(4): 275.

Surgery for endocarditis

Discuss early with the regional cardiothoracic centre: immediate intervention may be appropriate.

- Surgical intervention may be necessary, either during active infection or later because of the degree of valve destruction. Optimal timing depends on a number of factors:
 - haemodynamic tolerance of the lesion
 - outcome of the infection
 - presence of complications.
- The choice of antimicrobial therapy should be modified depending on microbiological results from intraoperative specimens. Samples should be sent for culture, staining, immunological testing, and PCR, depending on the suspected organism.
- The duration of antimicrobial treatment is dependent on the clinical picture:
 - culture-negative operative specimens: 2–3 weeks for valve infection and 3–4 weeks for abscess.
 - culture-positive operative specimens: 3–4 weeks for valve infection and 4–6 weeks for abscess.
- Timing is dictated by the clinical picture. American College of Cardiology/American Heart Association (ACC/AHA) indications for surgery are listed in Table 4.2. In patients with neurological injury, surgery should be delayed to avoid intracranial hemorrhage if cardiac function permits (embolic infarct—delay 10–14 days, haemorrhage 21–28 days and when ruptured mycotic aneurysms have been repaired).

Timing of surgery (see Table 4.2)

- If the patient is haemodynamically stable, surgery may be delayed until after the antibiotic course is completed. The final management depends on the valve affected, the degree of destruction, and its effect on ventricular function. Severe aortic and mitral regurgitation usually require surgery; tricuspid regurgitation, if well tolerated, is managed medically.
- Decompensation (severe congestive cardiac failure or low cardiac output syndrome with functional renal failure) may respond to surgery, but the mortality is high.
- 'Metastable' patients who have been successfully treated after an episode of acute decompensation should be considered for early operation after 2–3 weeks' antibiotic therapy.
- The onset of complications listed opposite is an indication for early surgery

Outcome of infection

- Persistence or relapse of infection (clinical and laboratory indices) despite appropriate antibiotics at an adequate dose may be due either to a resistant organism or to an abscess (paravalvular, extracardiac). Consider valve replacement if no extracardiac focus is found.
- The organism may influence the decision: consider early surgery for fungal endocarditis or prosthetic endocarditis with *E. coli* or *S. aureus*.

The presence of complications

- High-degree AV block
- Perforation of interventricular septum
- Rupture of sinus of Valsalva aneurysm into right ventricle (RV)
- Intracardiac abscess
- Prosthetic endocarditis, especially associated with an unstable prosthesis

Surgical options

- The presence of annular abscess makes surgery technically more challenging.
- Mitral and tricuspid endocarditis: competent valve repair (rather than replacement) is the best solution, minimizing prosthetic material, maximizing freedom from reoperation. It may be technically challenging.
- Aortic valve: annular abscess may require root replacement
- Additional risk of operative mortality associated with endocarditis is 2–5%, with significant additional risk if the patient presents in cardiogenic shock or after prolonged hospital stay.

Table 4.2 Indications and timing of surgery in left-sided native valve infective endocarditis

Recommendations: Indications for surgery	Timing^a
A. Heart failure	
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock	Emergency
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock	Emergency
Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent
Aortic or mitral IE with severe regurgitation and no HF	Elective
B. Uncontrolled infection	
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent
Persisting fever and positive blood cultures >7–10 days	Urgent
Infection caused by fungi or multiresistant organisms	Urgent/elective
C. Prevention of embolism	
Aortic or mitral IE with large vegetations (>10 mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent
Aortic or mitral IE with large vegetations (>10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent
Isolated very large vegetations (>15mm) ^b	Urgent

^aEmergency surgery: surgery performed within 24 h, urgent surgery: within a few days, elective surgery: after at least 1 or 2 weeks of antibiotic therapy.

^bSurgery may be preferred if a procedure preserving the native valve is feasible.

Reproduced from Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis (new version 2009). The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* **30**: 2369–413. □ <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-IE-FT.pdf>

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Endocarditis prophylaxis

Key facts


- ACC/AHA guidelines on endocarditis prophylaxis were updated in 2008 to reflect consensus opinion that routine antibiotic prophylaxis is not indicated in the majority of what were previously considered at-risk patients for procedures such as dental work, endoscopy, etc.
- Although reducing antibiotic use might provide important population benefit in the form of reducing evolution-resistant species, in view of the risk:benefit ratio at the individual level, many clinicians continue to prescribe prophylaxis according to earlier guidelines (see Tables 4.3 and 4.4)
-  Presentation of endocarditis, Table 4.1, p. 195 shows cardiac conditions at risk of IE. High and moderate risk requires prophylaxis; 'low' risk does not.
- The regimen may be modified, depending on the 'degree of risk' (both patient and procedure related) as shown in the box below.

Table 4.3 Recommendations for prophylaxis of infective endocarditis in highest-risk patients according to the type of procedure at risk

Recommendations: prophylaxis

A. Dental procedures:

Antibiotic prophylaxis should only be considered for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa

Antibiotic prophylaxis is not recommended for local anaesthetic injections in non-infected tissue, removal of sutures, dental X-rays, placement or adjustment of removable prosthodontic or orthodontic appliances or braces. Prophylaxis is also not recommended following the shedding of deciduous teeth or trauma to the lips and oral mucosa

B. Respiratory tract procedures^a:

Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, transnasal or endotracheal intubation

C. Gastrointestinal or urogenital procedures^a:

Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy, or transoesophageal echocardiography

D. Skin and soft tissue^a:

Antibiotic prophylaxis is not recommended for any procedure

^a For management when infections are present, please refer to the text.


Reproduced from Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009). The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). *Eur Heart J* 30: 2369–413.  <http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-IE-FT.pdf>

Table 4.4 Antibiotic prophylaxis

Minimal regimen		
	1 h before	6 h after
No penicillin allergy	Amoxicillin 3 g PO	No 2nd dose
Allergy to penicillin	Clindamycin 300–600 mg PO	No 2nd dose
<i>Flexible modifications depending on the 'degree of risk'</i>		
<ul style="list-style-type: none"> • Additional doses after procedure • Additional aminoglycosides • Parenteral administration 		
Maximal regimen		
	1 h before	6 h after
No penicillin allergy	Amoxicillin 2 g IV	1–1.5 g PO
	+ Gentamicin 1.5 mg/kg IM/IV	No 2nd dose
Allergy to penicillin	Vancomycin 1 g IV over 1 h	1 g IV at 12 h
	+ Gentamicin 1.5 mg/kg IM/IV	No 2nd dose

Outpatient review

Be very wary about discharging patients from routine follow-up.


General considerations

Valvular heart disease tends to worsen with time. Consequently, long-term follow up is the norm rather than the exception. Very minor lesions (e.g. mild mitral, aortic, or tricuspid regurgitation) with no symptoms are relatively benign and do not need regular review.

Symptoms review

Has there been any progression since last review (NB: can be insidious and patients often don't notice—ask about specific activities and whether they can still do them as well as before). Are there any new symptoms (particularly chest pain, dyspnoea, palpitations, syncope)? Are there any symptoms to suggest endocarditis (fevers, weight loss, malaise, joint, or back pains)? When did they last visit the dentist and are they aware of need for prophylaxis? Ask about medications (what are they on, have there been any additions or dose changes? If so, why?). Review anticoagulation and antiplatelet therapy: is there an indication, is compliance adequate?

Examination

Look for peripheral stigmata of endocarditis (see  Chapter 5), record the rate and character of pulse and blood pressure (BP). Assess jugular venous pressure (JVP) and apex beat and then auscultate precordium and remember to listen to lung bases and to check for pedal oedema.

Investigation

Always review current ECG, TTE (\pm CXR) and compare with previous results to look for progression of condition. Consider haemoglobin/haematocrit and lactate dehydrogenase in patients with a prosthetic valve.

Specific conditions

With all conditions, patients should be advised to seek earlier review if symptoms change in the intervening period.

Mitral stenosis: If mild with no symptoms, can be reviewed every 2 years. Moderate to severe (or with symptoms) should be seen at least annually.

Mitral regurgitation (MR): Patients with asymptomatic mild MR can be reassured and discharged. Moderate to severe MR or with symptoms should be seen at least annually. If LV dimensions start to enlarge or ejection fraction (EF) declines, consider referral for surgery.

Aortic stenosis (AS): Asymptomatic patients with mild AS should be seen every 2–3 years. Anything greater than moderate AS or with symptoms should be seen annually. Mild AS: ECHO every 3–5 years; moderate AS: ECHO every 1–2 years. In severe AS or patients with moderate AS and symptoms, work-up for aortic valve replacement (AVR) should be commenced.

Aortic regurgitation (AR): Asymptomatic patients with mild AR can be reassured and discharged. Patients with symptoms or moderate AR should be seen at least annually. If LV starts to dilate or severe AR, refer for consideration of AVR.

Prosthetic valves: See annually. After >8 years, review patients with bioprostheses every 6 months (↑incidence of valve failure). If new valvular dysfunction is detected, then investigate promptly (often requiring admission), as this can dramatically worsen very rapidly. Once regurgitation is detected, close follow-up with 2D and Doppler echocardiography every 3 to 6 months is indicated.

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Atherosclerosis: pathophysiology

Atherosclerosis is a disease of the large and medium-sized arteries. The term atherosclerosis is derived from Latin and means gruel-like ('athero') hardening ('sclerosis') of the arteries. The disease is characterized by a gradual build up of fatty plaques within the arterial wall, which eventually results in a significant reduction of the vessel lumen, impairing blood flow to the distal tissues. These plaques may also cause acute coronary syndromes by becoming unstable and triggering coronary thrombosis.

Pathophysiology

The atherogenic process is characterized by:

- dysfunction of the endothelial lining of the vessel
- inflammation of the vascular wall
- build up of lipids, cholesterol, and inflammatory cells in the vessel wall
- accumulation of cellular debris within the intima and subintimal layers of the vessel.

These processes result in plaque formation, and remodelling of the arterial wall. The underlying mechanisms are uncertain, but the most widely accepted theory is the 'response-to-injury' hypothesis defined by Ross in the 1970s.

Endothelial dysfunction

The initiating trigger of this disease process appears to be injury of arterial endothelial cells from exposure to stimuli including:

- tobacco toxins
- oxidized low-density lipoprotein (LDL)
- advanced glycation end-products
- elevated homocysteine
- infectious agents.

Endothelial cell injury initiates a cascade of events resulting in cellular dysfunction (see Fig. 5.1). The hallmark of endothelial dysfunction is a change in the balance of production of endothelium-derived vasoactive molecules:

- reduced bioavailability of endothelial nitric oxide (NO), an important vasodilator, anti-thrombotic, and antiproliferative agent
- increased generation of potent vasoconstrictor agents endothelin-1 and angiotensin-II, promoting cell migration and growth
- dysfunctional endothelial cells express adhesion molecules and secrete chemokines, promoting cell migration and adhesion
- local thrombotic balance is altered as levels of plasminogen activator inhibitor (PAI) and tissue factor are increased
- tissue plasminogen activator (t-PA) and thrombomodulin are reduced
- low NO release results in increased platelet activation and adhesion.

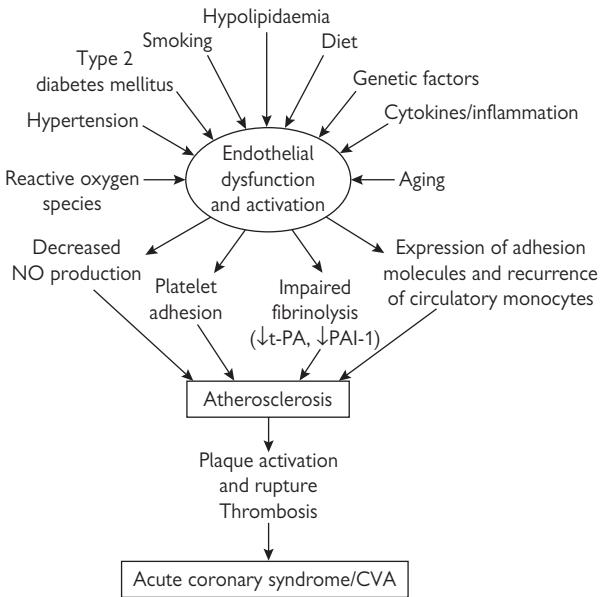


Fig. 5.1 Endothelial dysfunction is the underlying process in atherosclerosis, from lesion initiation and progression, through to acute cardiovascular events. Endothelial dysfunction is caused by a variety of genetic factors (and aging), as well as environmental factors that can be modified. CVA = cerebrovascular accident.

Development of atherosclerotic plaques

Endothelial dysfunction creates a local milieu, which facilitates the initiation and development of the atherogenic process (see Fig. 5.2).

- Circulating leucocytes, predominantly monocytes, are attracted and bind to activated endothelial cells, followed by migration into the subendothelial layer, where they transform into macrophages.
- They act as local 'scavenger' cells with the capacity to take up modified LDL cholesterol (LDL-C), ultimately becoming the characteristic 'foam cells' of established atherosclerosis.
- The earliest lesions are known as 'fatty streaks', which consist predominantly of lipid-accumulating macrophages and foam cells.
- These lesions may develop into fibrous plaques, as a consequence of further lipid accumulation accompanied by local migration, proliferation, and fibrous transformation of smooth muscle cells.
- These cells are responsible for the deposition of extracellular connective tissue matrix, leading to formation of a fibrous cap, which overlies a central core, consisting of foam cells, extracellular lipid, necrotic cellular debris, and a mixture of other inflammatory cells including T-lymphocytes.
- This process is facilitated by ongoing endothelial dysfunction, together with local generation of powerful mitogens such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), and insulin-like growth factor (IGF) from endothelial cells, macrophages, and activated platelets.
- Further growth of the plaque initially causes outward remodelling of the vessel wall, minimizing the impact on the cross-sectional area of the lumen and the vessel's ability to deliver blood.
- Progressive plaque accumulation results in luminal narrowing, and ultimately vessel obstruction.

Lesion initiation and progression tends to occur more predictably at certain locations of the vascular system.

- Blood flow through arteries causes local generation of fluid 'shear-stress', which influences the biology of the underlying endothelial cells.
- High laminar shear (from blood flowing quickly through a straight vessel) favours the generation of NO, which helps maintain the functional integrity of the vessel.
- In contrast, low shear, or 'differential' shear caused by turbulent flow, causes dysfunction of the underlying endothelial cells, which facilitates initiation and progression of atheroma.
- This helps explain why plaques are found more commonly at sites of vessel branching or curvature, which experience more dramatic and abrupt changes and irregularities of direction and velocity of blood flow.
- These shear-stress-mediated effects are most marked in vessels that carry a high (basal) blood flow, such as the coronary, carotid, renal, and ilio-femoral arteries, in which the majority of clinically important atherosclerotic lesions develop.

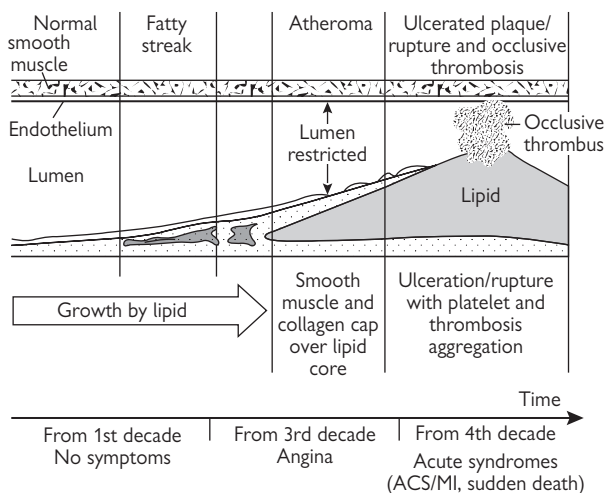


Fig. 5.2 Cellular interactions in the development and progression of atherosclerosis. VSMC, vascular smooth muscle cells. ACS = acute coronary syndrome; MI = myocardial infarction. Reproduced with permission from Weissberg PL (2003). *Atherogenesis: current understanding of the causes of atheroma. Heart* **83**: 247–52.

Epidemiology

Cardiovascular disease is the most common cause of death in the UK, responsible for 238 000 deaths in 2002 or 39% of all deaths. Coronary artery disease (CAD) results in over 117 000 deaths a year in the UK. Advances in prevention and treatment of this disease have led to a fall in the death rate since the late 1970s, but the UK incidence of CAD remains amongst the highest in the world. The cost of health care alone is estimated at over £1.7 billion a year, and the total economic cost is far greater.

Regional variation

There is considerable variation in mortality from CAD across the UK. Death rates are higher in Scotland than the South of England, in manual workers than in non-manual workers, and in certain ethnic groups. There are several important risk factors that are associated with CAD and other atherosclerotic disease (see [Risk factors for coronary artery disease](#), p. 220), which together account for the majority of the CAD burden in the UK. Although identification and treatment of individuals with these risk factors has the potential to reduce significantly the burden of CAD, the incidence of and death rate from MI remain high.

The vulnerable plaque

Erosion or denudation of the endothelial layer, or rupture of the overlying fibrous cap of the plaque may expose the highly thrombogenic lipid-rich core of the plaque to circulating blood.

- Collagen, tissue factor, and other factors activate platelets and trigger the coagulation cascade.
- This leads to acute thrombosis, which may rapidly occlude the vessel.
- This results in MI of this vascular territory, usually characterized by ST-segment elevation on the electrocardiogram (ECG).
- Coronary thrombosis is a dynamic process *in vivo*, and may be reversed, at least in part, by activation of t-PA and proteins C and S of the intrinsic antithrombotic/fibrinolytic system.
- Acute, subtotal occlusion of the vessel typically causes acute symptomatic deterioration and non-ST-segment elevation MI (NSTEMI) or unstable angina.
- Atheromatous plaques that have a thin fibrous cap and a large necrotic lipid core, and contain a high proportion of inflammatory cells and mediators, and are particularly predisposed to destabilization or rupture, with consequent thrombosis.
- Conversely, plaques with a smaller lipid pool, thicker fibrous caps, and less inflammatory activity are more stable and less prone to rupture.
- Several studies have shown that well over half of all MIs are caused by acute destabilization of plaques that were previously not obstructing flow in the vessel, suggesting that the likelihood of an acute coronary event is more closely related to the stability of the plaque rather than the severity of the stenosis.

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Assessment of atherosclerotic risk

Identification and treatment of risk factors is essential for the prevention of atherosclerotic disease in both individuals and society. When multiple risk factors such as dyslipidaemia, high blood pressure, and smoking co-exist, the cardiovascular risk is greatly increased, suggesting a synergistic interaction between these factors.

Global risk assessment

Risk-assessment scoring systems are derived from large prospective population cohorts, most commonly the Framingham study. These systems allow calculation of the 'absolute risk' of having a cardiovascular event (i.e. the probability of having a heart attack or stroke) within the next 10 years. Current UK practice recommends use of the Joint British Societies risk-assessment tables (see Fig. 5.3) or a computer program. Other commonly used methods include:

- the Framingham risk-scoring system
- the Sheffield tables
- the European SCORE charts.

Subjects with stable angina have a 10-year event rate of approximately 20%; therefore, subjects without clinical disease that have a predicted 10-year likelihood of suffering a cardiovascular event of $\geq 20\%$ are considered to be at 'high risk' and are candidates for aggressive risk-factor management.

Individuals with low-intermediate risk—scoring systems typically underestimate the true risk in:

- young subjects with multiple risk factors
- subjects with a family history of premature cardiovascular disease
- certain ethnic groups including individuals of South Asian racial origin living in the UK.

Identification of subjects with intermediate (10–20%) conventional risk scores that are actually at 'high' risk remains a major challenge, as these individuals are also likely to benefit from preventive therapy.

Adjunctive risk-assessment techniques may improve risk-assessment accuracy but are not currently used in routine clinical practice:

- C-reactive protein (CRP) levels
- ultrasound assessment of carotid arterial intima-media thickness
- detection of coronary artery calcification with computed tomography (CT) scanning.

- Calculation of risk is unnecessary in subjects who already have clinical atherosclerotic disease, as secondary prevention measures are mandatory in these individuals.
- Similarly, risk calculation is not required for subjects with diabetes mellitus, whose risk approaches that of subjects with established atherosclerosis.

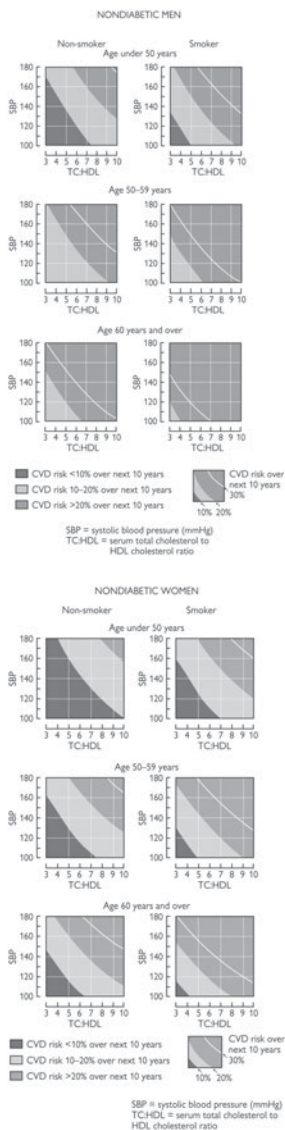


Fig. 5.3 Reproduced with permission from 2004 Joint British Societies Risk Prediction Tables. © The University of Manchester. CVD = cardiovascular disease.

Risk factors for coronary artery disease

Age

The UK population is aging:

- between 1971 and 2002, the percentage of older people (aged 65 years and over) in the UK, increased from 13% to 16%, and is projected to rise to 23% in the next 25 years
- aging is a major risk factor for atherosclerotic disease, due to the degenerative process associated with aging *per se*, together with the cumulative impact of the worsening risk-factor profile that develops with increasing age
- by the age of 70 years, 15% of men and 9% of women have symptomatic CAD, increasing to 20% by the age of 80 years
- Over 40 000 premature (<75 years) deaths are caused by CAD, 22% of premature deaths in men and 13% of those in women
- 45% of MI occurs in people under 65 years of age but is more likely to be fatal in older individuals, with 80% of deaths due to MI seen in those aged over 65 years.

Gender, menopausal status, and hormone replacement therapy (HRT)

- CAD is more common in men than women and the onset tends to be earlier in men.
- The incidence of coronary heart disease (CHD) in women increases rapidly at menopause, and is similar to that seen in men in the population over 65 years.
- Although less common, the disease remains one of the biggest killers of women; for example, the age-adjusted mortality rates from heart disease are four to six times higher than their mortality rates from breast cancer.
- Female sex hormones probably contribute to the lower risk of atherosclerotic disease in premenopausal women.
- The risk of ischaemic heart disease is reduced by up to 40% in women using HRT. HRT users are typically healthier than non-users, suggesting that these results could be explained by selection bias.
- Several large, randomized controlled trials of HRT in postmenopausal women (WHI (Women's Health Initiative), HERS (Heart and Estrogen/ Progestin Study)/HERS II, ESPRIT (Estrogen in the Prevention of Reinfarction Trial), ERA (Estrogen Replacement and Atherosclerosis)) with and without atherosclerosis have now clearly shown that HRT does not reduce the risk of cardiovascular events.
- HRT may, in fact, even lead to a small but statistically significant increase in morbidity and mortality from cardiovascular and other diseases including gynaecologic malignancy.
- *HRT should not be recommended for primary or secondary prevention of atherosclerotic disease in postmenopausal women.*

Family history of atherosclerotic disease

- CAD is a multifactorial, polygenic disorder, caused by interactions between lifestyle, the environment, and the effects of variations in the genetic sequence of a number of genes.
- The family history is considered to be significant when atherosclerotic disease presents in a first-degree male relative before the age of 55 years, or before 65 years in a female relative.
- A positive family history is associated with a 75% increase in risk in men, and an 84% increase in women. The risk is more than doubled if both parents are affected.

Risk factors for coronary artery disease

Non-modifiable risk factors

- Increasing age
- Male sex
- Family history
- Ethnic origin

Modifiable risk factors

- Smoking
- High blood pressure
- Dyslipidaemia
- Diabetes mellitus
- Obesity and the metabolic syndrome
- Psychological stress
- High-calorie high-fat diet
- Physical inactivity

Emerging risk factors

- Inflammation
- Fibrinogen, and other factors involved in thromboregulation
- Homocysteine
- Oxidative stress
- Asymmetric dimethylarginine

Ethnic origin

- Age-standardized mortality from CAD is around 50% higher in individuals of South Asian racial origin living in the UK compared to white individuals.
- Although an increased prevalence of risk factors explains much of this risk (high triglycerides, low high-density lipoprotein (HDL), insulin resistance, and reduced physical activity), genetic factors are thought to contribute significantly.
- The observed incidence of CAD is lower in black individuals of West Indian and African origin in the UK, although the incidence of stroke is greater than in the Caucasian population.

Psychological stress

- The burden of risk attributable to psychological stress is more difficult to quantify.
- Increased work stress, lack of social support, hostile personality type, anxiety, and depression are most consistently associated with increased atherosclerosis risk.

Smoking

- Smoking increases the risk of CAD by approximately 50%, with mortality from any cardiovascular disease around 60% higher in smokers (and 85% higher in heavy smokers) compared to non-smokers.
- In the UK today, around 13 million adults (28% of men and 26% of women) smoke cigarettes.
- Although the number of smokers has declined substantially over the past 50 years, this trend has slowed down in the young, and the number of teenage girls that smoke has recently increased.
- Over 30 000 cardiovascular deaths per year (14% in men and 12% in women, with an even higher proportion of premature deaths) are attributable to smoking.
- Second-hand smoke (smoke that has been exhaled by a smoker) can also increase the risk of CAD by around 25%.
- Stopping smoking carries almost immediate benefit, and although the long-term benefits are greatest in those who stop smoking before the age of 40 years, stopping in middle age is also beneficial. For example, in those aged 30–59 years who stop smoking after a MI, the 5-year mortality is 10%, compared with 14% in those who continue to smoke.
- Individuals at increased risk of atherosclerosis should be advised to stop smoking. See Figs. 5.4. and 5.5.
- Evidence now exists that focused psychosocial support, nicotine replacement, and pharmacological therapy are effective in helping individuals stop smoking. These services are delivered in an integrated fashion by smoking-cessation clinics, which can deliver a fourfold increase in the likelihood that a smoker will quit, vs. use of willpower alone.

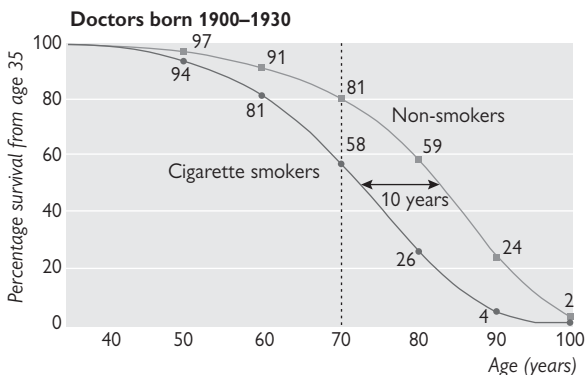


Fig. 5.4 Survival from age 35 years for continuing cigarette smokers and lifelong non-smokers among UK male doctors born 1900–1930, with percentages alive at each decade of age (adapted and reproduced with permission from Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 328(7455): 1519).

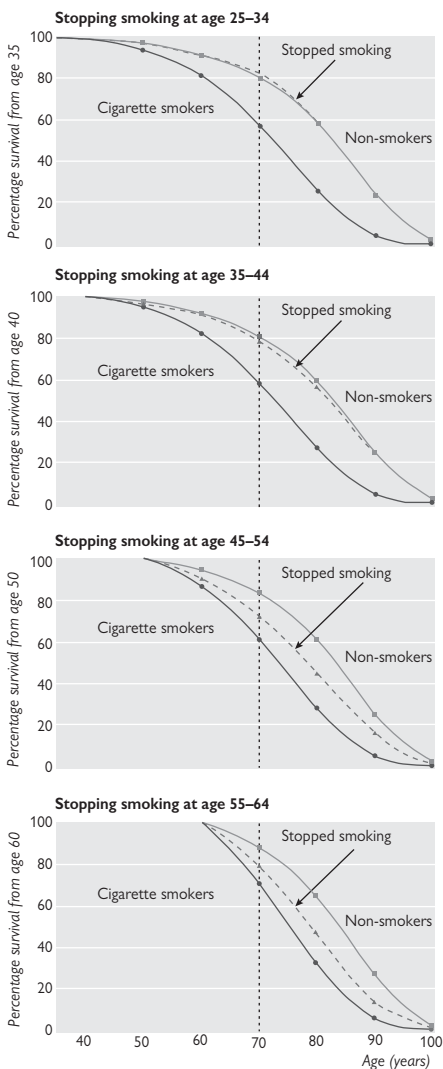


Fig. 5.5 Effects on survival of stopping smoking cigarettes at age 25–34 years (effect from age 35 years), age 35–44 years (effect from age 40 years), age 45–54 years (effect from age 50 years), and age 55–64 years (effect from age 60 years) (adapted and reproduced with permission from Doll R, Peto R, Boreham J, Sutherland I (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 328(7455): 1519).

Obesity

- Obesity increases the risk of CAD: 25–49% of CAD in developed countries is attributable to increased body mass index (BMI).
- Overweight is defined as a BMI between 25 and 30 kg/m², and obesity as a BMI ≥30 kg/m².
- The prevalence of obesity is increasing rapidly worldwide. In the UK, adult obesity has increased by over 50% in less than 10 years.
- Of particular concern is the dramatic increase in the prevalence of obesity in children, which has almost doubled in the UK in less than 10 years. This trend is likely to exacerbate the problem in adulthood, and undo many of the other recent improvements in cardiovascular health.
- Central obesity, in which excess fat is concentrated mainly in the abdomen, can be identified by a high waist-to-hip ratio, and confers a particularly high relative risk of CAD if the waist circumference is >102 cm (40 in.) in men and >88 cm (35 in.) in women.
- Associated metabolic abnormalities of central obesity include high triglycerides, low HDL, high blood pressure, low-grade systemic inflammation, insulin resistance, and type 2 diabetes mellitus.
- Overweight and obese individuals also tend to be less physically active and eat lower-quality diets, which contributes further to their atherogenic risk.
- Diet and exercise should be considered as the first line of intervention in these individuals, together with careful surveillance for and aggressive treatment of diabetes, high blood pressure, and dyslipidaemia when present.

Inflammation

- Atherosclerosis involves an ongoing inflammatory process from the time of lesion initiation, through progression and at the time of acute thrombotic complication.
- This links risk factors and the disease mechanism in a way that is directly applicable to human patients.
- Large studies have shown that low-grade elevation in markers of inflammation, most notably CRP, predicts outcomes from atherosclerotic disease and may add to prognostic information provided by traditional risk factors.
- A CRP level below 1 mg/L is associated with low risk, 1–3 mg/L reflects intermediate risk, and a level above 3 mg/L is associated with a high long-term risk of vascular events.
- Certain treatments that reduce coronary risk also limit inflammation, such as statins and aspirin, which may contribute to their clinical benefits.
- The incremental value of CRP as a marker of risk and target of therapy in global risk management is currently a controversial topic that requires clarification by prospective randomized trials.

Homocysteine

- The genetic disease homocystinuria is associated with aggressive, premature atherosclerosis.

- Strong epidemiologic and mechanistic evidence suggests that even modest increases in homocysteine levels increase the progression of atherosclerosis.
- Vascular inflammation and oxidative stress appear to be the responsible mechanisms.
- Dietary supplementation with folic acid, alone or in combination with vitamins B₆ and B₁₂, can reduce levels of homocysteine and improve aspects of vascular biology *in vivo* as well as *in vitro*.
- Until results of large, outcome-driven, randomized clinical trials are available, folate ± B₆/B₁₂ supplementation cannot be routinely recommended for prevention of atherosclerotic disease.

Antioxidant vitamins

Despite excellent epidemiologic and mechanistic evidence that increased oxidative stress is associated with vascular injury, inflammation, and increased risk of cardiovascular morbidity and mortality, it is disappointing that large randomized controlled trials (HOPE (Heart Outcomes Prevention Evaluation), HPS (Heart Protection Study) and GISSI-P (Gruppo Italiano per lo studio della Sopravvivenza nell'infarto Miocardico)) showed that supplementation with the antioxidant vitamin E (supplemented with vitamins A and C in HPS) had no effect on cardiovascular outcome. Currently, antioxidant vitamin supplementation should not be routinely recommended for prevention of atherosclerotic disease.

Dietary measures

Dietary modification can reduce the risk of cardiovascular disease:

- total fat intake should be reduced to below 30% of total calorie intake
- intake of saturated fat and foods high in 'trans' fatty acids should be limited, and replaced with monounsaturated fat (canola and olive oil)
- dietary salt intake should be reduced
- intake of fresh fruits and vegetables should be increased (≥5 portions per day)
- fish consumption, especially oily fish, should be encouraged, with evidence suggesting that at least one fish meal, and ideally 2–3 per week can reduce the incidence of heart attack and stroke.

Physical activity

- The contribution of physical inactivity to CAD deaths is difficult to quantify; however, people who are physically active appear to have a lower risk of CAD.
- This is mediated, at least in part by weight loss, a reduction in blood pressure, and improvement of the lipid profile (particularly increased HDL).
- Regular, aerobic exercise of moderate intensity should be undertaken ≥3 times per week for at least 30 minutes, but greater frequency and duration of exercise is associated with increasing benefits.

Alcohol

Moderate alcohol consumption (one or two drinks per day) is associated with a reduced risk of CAD, whereas higher levels of alcohol intake (in excess of 21 units/week for men or more than 14 units/week) in women, particularly in 'binges', is associated with an increased risk of CHD.

Hypertension

Definition

A continuous relationship exists between increasing blood pressure and cardiovascular risk; therefore, it is impossible to define hypertension precisely. For practical purposes, levels of blood pressure above which the risk increases significantly, and treatment can provide a clear-cut benefit, are used as a working definition of hypertension (see Table 5.1). The average of two readings at each of a number of visits should be used to define the blood pressure.

Causes of hypertension

The majority of subjects (>95%) have essential (primary) hypertension, in which an underlying cause for the hypertension is not found.

There are many causes of secondary hypertension (see Table 5.1).

Symptoms and signs

Hypertension is usually asymptomatic, although a patient will occasionally complain of headache. A history of cardiac or neurologic symptoms should always be sought. The cardiovascular system should be examined in detail, and fundoscopy should be performed to look for retinopathy (see Table 5.1).

Clinical signs of an underlying cause (radiofemoral delay or weak femoral pulses, renal enlargement or bruit, or cushingoid features) and evidence of end-organ damage (heart failure, retinopathy, aortic aneurysm, carotid or femoral bruit) should be sought.

Malignant hypertension is diagnosed when severe hypertension (systolic blood pressure (SBP) >200 mmHg \pm diastolic blood pressure (DBP) >130 mmHg) is identified, together with grade III–IV retinopathy.

- The patient often has a headache and occasionally visual disturbance.
- Proteinuria and haematuria are often present.
- This is a medical emergency requiring immediate treatment to prevent rapid progression to renal failure, heart failure, and/or stroke.
- Untreated, the 1-year mortality is approximately 90%.

Investigation

Important investigations in all patients presenting with hypertension are:

- ECG
- fasting glucose
- full lipid profile (total, HDL and LDL cholesterol and triglycerides)
- urea and electrolytes (U&E)
- urinalysis for blood and protein

If secondary hypertension is suspected, further investigation should focus on the possible underlying cause (e.g. urinary cortisol, plasma renin-aldosterone levels, renal ultrasound, magnetic resonance angiography (MRA) of renal arteries, MAG3 renogram, and 24-hour urinary catecholamines or vanillyl mandelic acid (VMA)).

Table 5.1 Blood pressure (BP) classification

Category	SBP (mmHg)	DBP (mmHg)
Optimal BP	<120	<80
Normal BP	<130	<85
High-normal BP	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110

Adapted from British Hypertension Society (2004). <http://www.bhsoc.org>

Secondary hypertension (<5%)

Renal disease

- Diabetic nephropathy, renovascular disease, glomerulonephritis, vasculitides, chronic pyelonephritis, polycystic kidneys

Endocrine disease

- Conn's and Cushing's syndromes, glucocorticoid-remediable hypertension, pheochromocytoma, acromegaly, hyperparathyroidism

Other

- Aortic coarctation, pregnancy-induced hypertension and pre-eclampsia, obesity, excessive dietary salt or licquorice intake, drugs (non-steroidal anti-inflammatory drugs (NSAIDs), sympathomimetics, illicit stimulants, e.g. amphetamine, MDMA ('ecstasy'), and cocaine

Grading of hypertensive retinopathy

- I. Tortuous arteries, with thickened bright walls ('silver wiring')
- II. Arteriovenous nipping (narrowing in a vein where crossed by an artery)
- III. Flame haemorrhages and cotton wool spots (small retinal bleeds and exudates)
- IV. Papilloedema

Treatment of high blood pressure

When to treat

- Patients with malignant hypertension or with persistent BP > 160/100 mmHg after lifestyle measures
- Subjects with BP > 140/90 mmHg after lifestyle measures who have evidence of end-organ damage (left ventricular hypertrophy (LVH) on ECG, proteinuria or retinopathy) or a calculated 10-year risk of a cardiovascular event $\geq 20\%$
- Subjects who have clinical evidence of CAD, peripheral or cerebrovascular disease if BP > 140/90 mmHg.

Blood pressure targets

- Most patients should have their BP lowered to a target of < 140/85 mmHg.
- Patients with diabetes, have been shown to benefit from more aggressive BP reduction (UKPDS (UK Prospective Diabetes Study) and HOT (Hypertension Optimal Treatment) studies), and a target of < 130/80 mmHg is more appropriate.

Lifestyle measures

- Minimize dietary salt intake (< 100 mmol/day)
- Reduce alcohol to < 21 units (men) and < 14 units (women) per week
- Take regular aerobic exercise if not contraindicated (at least 30 min, 3x/week)
- Achieve and maintain healthy BMI (20–25 kg/m²)
- Consume at least 5 portions/day of fresh fruit and vegetables
- Stop smoking, and reduce dietary fat content, especially saturated and trans-fatty acids.

Uptake of these lifestyle measures is often difficult to sustain, and implementation is most successful in a multidisciplinary professional setting when supported by clear written information, including individualized strategies and goals.

Choice of drug therapy

Large meta-analyses of studies of BP-lowering therapy have clearly shown that the degree of blood pressure lowering is the best determinant of risk reduction. Comparative studies, such as ALL-HAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack), have typically shown that there is little evidence favouring one class of drug over another with respect to overall cardiovascular outcome.

- Thiazide diuretics are effective and cheap and widely recommended as first-line antihypertensive therapy.
- Although calcium-channel blockers may be less protective than other agents against the development of heart failure, their safety and effectiveness in preventing atherosclerotic events is now confirmed, despite previous concerns.

- Treatment with the angiotensin receptor blocker (ARB) losartan demonstrated a small advantage, particularly in reducing stroke, compared to beta-blocker therapy in high-risk hypertensive patients with LVH (LIFE (Losartan Intervention for Endpoint reduction) study).

Compelling indications for specific class of antihypertensive agents

See Table 5.2.

Table 5.2 Indications for antihypertensive drugs

Class of drug	Compelling indication
Alpha-blocker	Benign prostatic hypertrophy
Angiotensin-converting enzyme inhibitors (ACE-Is)/ARBs	Heart failure/LV-dysfunction Established CAD Type 1 diabetic nephropathy, secondary stroke prevention ACE-I intolerant (ARB indicated) Type 2 diabetic nephropathy Hypertension + LVH
Beta-blockers	MI Angina Heart failure
Calcium-channel blockers	Elderly Systolic hypertension Angina
Thiazide diuretics	Elderly Heart failure Systolic hypertension

Adapted from British Hypertension Society (2004). <http://www.bhsoc.org>

Combining antihypertensive drugs

Most hypertensive individuals require more than one drug to control their blood pressure. Combining drugs at an earlier stage in the up-titration of therapy often results in better control with fewer side-effects than maximizing the dose of individual agents.

The British Hypertension Society has produced a practical algorithm that helps guide appropriate combination of antihypertensive drugs in clinical practice (see Table 5.3).

- This is based on the A-B-C-D principle (A = ACE-I or ARB, B = β -blocker, C = calcium-channel antagonist, D = diuretic).
- A or B are effective first-line drugs in the young, who typically have high-renin hypertension that responds well to these drug classes.
- C or D are more effective first-line agents in the elderly and black individuals, who typically have lower levels of renin and are less responsive to these agents.
- Drugs can be substituted or added in a stepwise fashion according to the response, until BP is controlled.
- Care should be taken if prescribing B + D together, as this combination may slightly increase the incidence of type 2 diabetes. ACE-I and ARB therapy can both reduce risk of developing this condition.

Other therapy

- The lipid-lowering arm of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study was terminated early due to a sizeable reduction in major vascular events seen in patients with hypertension and 'average' cholesterol levels treated with atorvastatin 10 mg daily for less than 4 years.
- Aspirin 75 mg daily is recommended in hypertensive patients with evidence of clinical atherosclerotic disease or $\geq 20\%$ 10-year cardiovascular event risk, after adequate BP control is achieved ($<150/90$ mmHg).
- Statin therapy should be initiated in these high-risk individuals, regardless of baseline cholesterol levels.
- Target lipid levels are total cholesterol (TC) <4.0 mmol/L, LDL-C <2.0 mmol/L, or a $>25\%$ or $>30\%$ reduction in TC or LDL-C respectively, whichever is the greater.

Table 5.3 Combining antihypertensive drugs: (The BHS A-B-C-D principle)

	<55 years and non-black	>55 years or black
STEP 1	A or B	C or D
STEP 2	A + C or D	
STEP 3	A (or B) + C + D	
STEP 4	Add β -blocker/spironolactone/or other diuretic	

Adapted from British Hypertension Society (2004). www.bhs.co.uk

Other drugs to consider include hydralazine, α -methyl dopa, clonidine, moxonidine, and minoxidil, but it is advisable that use of these drugs is supervised by a specialist.

Lipid management in atherosclerosis

Dyslipidaemia and risk of atherosclerosis

Numerous epidemiologic studies have confirmed that a direct relationship exists between cholesterol level and risk of CAD, even with the normal range of cholesterol. Increasing LDL-C levels appears to be the main driver of this pathologic relationship, but other atherogenic lipoprotein particles including very low-density lipoprotein (VLDL), chylomicron remnants, and lipoprotein(a) (Lp(a)) also appear to play an important role. LDL, particularly modified LDL, is recognized by the scavenger receptor on the surface of macrophages in the arterial wall, which take up these cholesterol-rich particles and eventually become the foam cells that form the lipid-rich core of atherosclerotic plaques. Increasing levels of HDL, involved in reverse cholesterol transport from the peripheries to the liver, protect against the development of atherosclerosis. Increased triglyceride levels are now also established as an independent risk factor for CAD. Emerging studies suggest that, in addition to the circulating lipid concentrations, the nature of the lipoprotein particles plays an important part in their atherogenic risk. For example, small dense LDL particles, as seen in subjects with diabetes, are more readily taken up by macrophages and appear to be more atherogenic than larger less-dense LDL.

Lipids and risk assessment

It is critical to consider the lipid profile in the context of the other risk factors present in the individual, by calculating 10-year cardiovascular risk. Although only TC and HDL-C are considered in most risk models, the levels of LDL and cholesterol and triglycerides should also be considered in the overall picture. Although blood should ideally be drawn for lipid analysis after a 12-hour fast, TC and HDL-C levels are only minimally affected by eating and are still valid in a non-fasting sample, unlike triglycerides and calculated LDL-C.

Measure a fasting lipid profile if the patient:

- is over 50 years of age
- has clinical atherosclerotic disease
- has \geq other risk factors for atherosclerosis
- has clinical signs of hyperlipidaemia (xanthomata, xanthelasmata, or corneal arcus at age <50 years)
- has a family history of premature CAD or hyperlipidaemia.

Most subjects at increased global risk of CAD have cholesterol levels between 4.0 and 6.5 mmol/dL, but a significant proportion of individuals have primary or secondary dyslipidaemic syndromes with characteristic abnormalities in the lipoprotein profile.

Normal ranges for plasma lipid levels

Total cholesterol	4.0–6.5 mmol/L	(150–250 mg/dL)
LDL cholesterol	<4.1 mmol/L	(<160 mg/dL)
HDL cholesterol	0.8–2.0 mmol/L	(30–75 mg/dL)
Triglycerides	0.8–2.0 mmol/L	(70–175 mg/dL)

Table 5.4 Primary hyperlipidaemias

Postscript roman numerals = WHO phenotype; chol/trig levels given in mmol/L.

Familial hyperchylomicronaemia (lipoprotein lipase deficiency or apoCII deficiency) ^I	Chol <6.5 Trig 10–30 Chylomicrons	↑	Eruptive xanthomata; lipaemia retinalis; hepatosplenomegaly
Familial hypercholesterolaemia ^{II} (LDL receptor defects)	Chol 7.5–16 Trig <2.3	LDL↑	Tendon xanthoma; corneal arcus; xanthelasma
Familial defective apolipoprotein B-100 ^{IIa}	Chol 7.5–16 Trig <2.3	LDL↑	Tendon xanthoma; arcus; xanthelasma
Common hypercholesterolaemia ^{IIa}	Chol 6.5–9 Trig <2.3	LDL↑	<i>The commonest 1° lipidaemia; may have xanthelasma or arcus)</i>
Familial combined hyperlipidaemia ^{IIb,IV or V}	Chol 6.5–10 Trig 2.3–12	LDL↑ VLDL↓ HDL↓	<i>Next commonest 1° lipidaemia; xanthelasma; arcus</i>
Dysbetalipoproteinaemia (remnant particle disease) ^{III}	Chol 9–14 Trig 9–14	IDL↑ HDL↓ LDL↓	Palmar striae; tuberoeruptive xanthoma
Familial hypertriglyceridaemia ^{IV}	Chol 6.5–12 Trig 3.0–6.0	VLDL↑	
Type V hyperlipoproteinaemia	Trig 10–30; chylomicrons		Eruptive xanthomata; lipaemia retinalis; hepatosplenomegaly

Primary HDL abnormalities

- Hyperalphalipoproteinaemia: ↑HDL, chol >2.
- Hypoalphalipoproteinaemia (Tangier disease): ↓HDL, chol <0.92.

Primary LDL abnormalities

- Abetalipoproteinaemia (ABL): trig <0.3, chol <1.3, missing LDL, VLDL and chylomicrons. Autosomal recessive disorder of fat malabsorption causing vitamin A & E deficiency, with retinitis pigmentosa, sensory neuropathy, ataxia, pes cavus and acanthocytosis.
- Hypobetalipoproteinaemia: chol <1.5, LDL↓, HDL↓. Autosomal codominant disorder of apolipoprotein B metabolism. ↑ longevity in heterozygotes. Homozygotes present with a similar clinical picture to ABL.

Chol = cholesterol; Trig = triglyceride.

Reproduced from Longmore M, Wilkinson I, Davidson E et al (2010). *Oxford handbook of clinical medicine*, 8th ed (2010). with permission from Oxford University Press. WHO = World Health Organization.

Secondary causes of dyslipidaemia

- Renal failure^a
- Nephrotic syndrome^a
- Hypothyroidism^a
- Type II diabetes and obesity^b
- Cholestasis
- Alcohol abuse
- Drugs:
 - anti-retroviral protease inhibitors
 - thiazides
 - oral contraceptive pill
 - isotretinoin
 - steroids

^aCholesterol elevation.

^bMinor elevation in cholesterol, but greater increases in atherogenic VLDL, chylomicron remnants, and triglycerides, as well as a fall in HDL.

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Lipid-lowering therapy

Statins

(e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin)

Statins reduce cholesterol levels by inhibiting HMG-CoA-reductase, the rate-limiting enzyme in cholesterol synthesis. They also:

- increase clearance of circulating LDL by upregulating LDL-receptor expression.
- are extremely effective at lowering cholesterol levels; for example, the most potent statins, atorvastatin and rosuvastatin can more than halve LDL-C levels at higher doses.
- increase HDL and decrease triglyceride levels.

A significant evidence base has been built up over the past decade that strongly supports the widespread use of statins in primary and secondary prevention, and confirmed their safety.

- Data from large randomized clinical trials have shown a consistent reduction (around 25–30%) in the relative risk of major cardiovascular events with the use of atorvastatin, pravastatin, and simvastatin in both the primary (ASCOT, WOSCOPS (West of Scotland Coronary Prevention Study), HPS, CARDS (Collaborative Atorvastatin Diabetes Study)) and secondary prevention settings (MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering), CARE (Cholesterol and recurrent Events), LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease), 4S (Scandinavian Simvastatin Survival Study), HPS).
- In the first outcome study comparing two statins, the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study showed that high-dose atorvastatin (80 mg) was more effective than pravastatin (40 mg) at preventing further major cardiovascular events during the first 2–3 years after presentation with an acute coronary syndrome.
- Typically, recommended evidence-based doses are simvastatin 40 mg nocte, pravastatin 40 mg od, and atorvastatin 10–80 mg od. Statins should not be prescribed to individuals with porphyria or severe liver or muscle disease, and caution is advised with their use in milder liver dysfunction, renal impairment, and in combination with fibrates.

Fibrates

(e.g. bezafibrate, ciprofibrate, fenofibrate, gemfibrozil)

- Fibrates improve the lipid profile by activating peroxisome proliferator-activated receptor alpha (PPAR- α), resulting in a mild lowering of TC and LDL-C.
- They also cause a significant reduction in triglycerides and increase in HDL.
- Subjects with combined hyperlipidaemia, or other reasons for a low HDL and/or high triglycerides, respond well to fibrates.
- The VA-HIT (Department of Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial) study showed that gemfibrozil (600 mg bd) reduced major cardiovascular events in subjects with average cholesterol and low HDL (<1.0 mmol/L) levels.

- Subgroup analysis of the HPS suggested that similar benefits were observed with simvastatin (40 mg) in such individuals.
- For the majority of patients, fibrates are typically recommended as second-line agents in patients who are intolerant of statins, particularly if they have low HDL or high triglycerides.
- The likelihood of liver or muscle side-effects is increased if a fibrate and statin are used in combination, and careful monitoring is recommended.
- The risk is lower if the statin is combined with fenofibrate than with other fibrates.

Anion-exchange resins

The agents colestyramine (4–8 g tds) and colestipol (5–10 g tds) bind bile salts in the small bowel. This inhibits their reabsorption, resulting in upregulation of the LDL receptor on hepatocytes and increased plasma cholesterol clearance. Although these drugs effectively lower cholesterol levels, most subjects experience intolerable gastrointestinal (GI) side-effects, limiting their widespread use. These drugs are generally recommended as second- or third-line therapy in subjects with hypercholesterolaemia.

Inhibitors of intestinal cholesterol absorption

The novel agent ezetimibe (10 mg od) binds to an intestinal cholesterol transport protein, which inhibits absorption. LDL-C is reduced by 15–20%. Ezetimibe is most effectively employed together with statin therapy in those patients who do not achieve cholesterol targets at higher statin doses, and is effective as monotherapy in those who are intolerant of statins.

Dietary plant stanols (3 g/day) can reduce LDL-C by up to 15%.

Nicotinic acid

Nicotinic acid (100–1000 mg tds, or 375–2000 mg modified-release (MR) preparation (Niaspan[®]) od) reduces hepatic VLDL synthesis and inhibits fatty acid release from adipocytes. HDL levels are significantly increased, and reduced hepatic synthesis results in a small reduction in LDL. Although particularly beneficial in mixed dyslipidaemias, use of the short-acting formulation has been limited by a high incidence of intolerable GI side-effects and facial flushing. The MR formulation is considerably more tolerable, and ongoing outcome studies should confirm the place of this agent in the preventive armamentarium.

Fish oils

Marine oil supplements containing high concentrations of omega-3 fatty acids are indicated for the treatment of severe hypertriglyceridaemia (Omacor[®] 4 capsules/day, Maxepa[®] 10 capsules/day). Omacor[®] (1 mg od, GISSI-P study) has a licence for secondary prevention post-MI, but the benefits observed with this dose do not seem to be due to lipid-lowering effects. An extensive clinical trial programme spanning a wide range of primary and secondary prevention settings should clarify the wider role of this drug in CAD prevention.

When to treat lipids

Therapeutic lifestyle changes (TLCs) are the first step in the treatment of dyslipidaemia. Moderate weight reduction (10% of body weight) improves the lipid profile and cardiovascular (CV) risk. The composition of the optimal diet is controversial.

General dietary recommendations include:

- reduced cholesterol and saturated fats (especially trans-fats)
- increased plant stanols, sterols, and soluble fibre
- adoption of Mediterranean diet.

Exercise should also be taken regularly.

Statin therapy should be initiated in all patients with established clinical atherosclerotic disease, including:

- CAD
- cerebrovascular disease
- renovascular disease
- peripheral arterial disease.

Current UK, European, and US guidelines also recommend statin therapy in subjects with:

- diabetes (CARDS, and subgroup analyses of HPS, ASCOT, and other major trials).
- CAD equivalent 10-year CV risk of $\geq 20\%$.

Although all of these patients should receive statins (unless contraindicated) regardless of their cholesterol level (HPS, ASCOT, CARDS), it is still important to measure lipid levels to ensure that subjects are responding appropriately to therapy and achieving targets for cholesterol < 4.0 mmol/L and LDL < 2.0 mmol/L. These targets are based on observations from clinical trials and cohort studies suggesting that 'lower is better' when it comes to cholesterol!

There is less outcome-based evidence informing us when to initiate drug therapy for isolated dyslipidaemia in the absence of other risk factors.

- Younger subjects without a family history of CAD or other risk factors should be considered for drug treatment if LDL-C > 5.0 mmol/L (or total > 7.0 mmol/L).
- Primary and familial hyperlipidaemias should be treated aggressively, particularly if there is a family history of premature CAD.

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Diabetes and atherosclerosis

Approximately 2 million people in the UK currently suffer from diabetes mellitus (DM), the vast majority of whom have type 2 diabetes (>90%). Although diabetes is more common in older individuals, the incidence is increasing at a dramatic rate in all age groups, especially young adults, driven by the obesity 'epidemic'. The prevalence of type 2 DM is also greater in black and South Asian individuals in the UK. Macrovascular disease is the most common cause of death in DM (>75%).

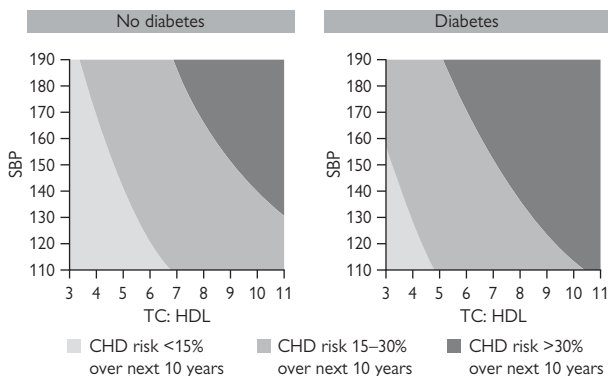


Fig. 5.6 The effect of type 2 DM on coronary heart disease (CHD) risk (non-smoker, age 60 years). Adapted from the British Cardiac Society, British Hyperlipidaemia Society, British Hypertension Society, British Diabetic Association (1998). *Heart* **80**(suppl 2): S1–S29.

Mechanisms responsible for increased CV risk in DM

A complex mix of risk factors is typically present in patients with diabetes including:

- low HDL
- high triglycerides (VLDL and remnant particles)
- increased small, dense LDL
- moderate hypertension
- low-grade inflammation
- a procoagulant state (increased PAI-1, and platelet activation)
- increased oxidative stress
- increased levels of harmful advanced glycation end-products.

Conventional risk factors only account for a relatively small proportion ($\approx 25\%$) of the increased risk observed in diabetes. Not only are subjects with diabetes more likely to suffer a major vascular event, they are also more likely to die from this event than if they did not have diabetes.

The atherosclerotic process tends to be more diffuse in individuals with diabetes, often affecting multiple vascular territories, making percutaneous and surgical revascularization more technically challenging and risky.

- Outcome is better when patients with diabetes and multivessel coronary disease undergo coronary artery bypass graft (CABG), rather than percutaneous revascularization (RITA (Radiofrequency Interstitial Tumour Ablation), BARI (Bypass Angioplasty Revascularization Investigation)).
- Data from large studies suggest that the outcome after percutaneous coronary intervention (PCI) in patients with diabetes is improved by use of drug-eluting stents as well as abciximab, a platelet glycoprotein (GP)IIb/IIIa antagonist.
- Visceral neuropathy is responsible for silent myocardial ischaemia, and reduced heart rate variability.
- Diabetic nephropathy further contributes to cardiac risk by increasing BP and causing deterioration in the lipid profile.

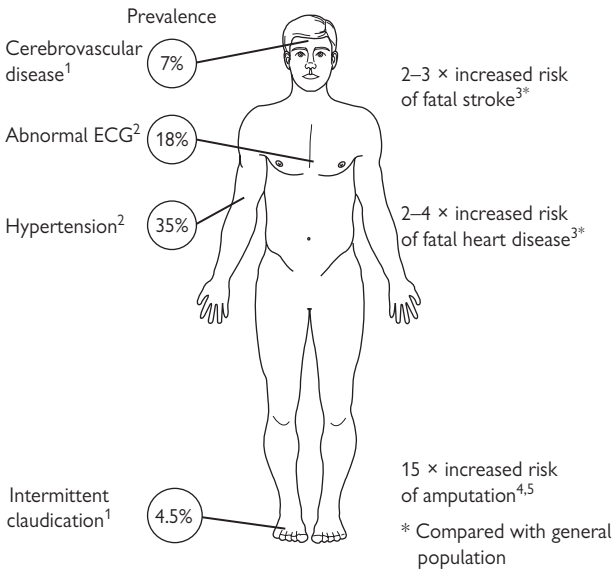


Fig. 5.7 Macrovascular disease in type 2 DM.

1 Wingard DL, Barrett-Connor EL, Scheidt-Nave C, McPhillips JB (1993). Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care* **16**: 1022–5.

2 UKPDS 6 (1990). Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Res* **13**: 1–11.

3 Balkau B, Pyörälä M, Shipley M et al (1997). Non-cardiovascular disease mortality and diabetes mellitus. *Lancet* **350**: 1680.

4 King's Fund (1996). *Counting the cost*. BDA.

5 Most RS, Sinnock P (1983). The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care* **6**: 87–91.

Recommendations for risk reduction in diabetes

Blood glucose should be aggressively controlled by means of diet and exercise coupled with appropriate intensity of hypoglycaemic drug therapy.

- Target glycosylated haemoglobin (HbA_{1c}) is $\geq 7\%$.
- Intense blood sugar control is better at reducing progression of microvascular disease and neuropathy than prevention of macrovascular events (UKPDS study).
- Aggressive blood pressure (UKPDS, HOT studies) and lipid management (CARDS, ASCOT, HPS) has a greater impact on prevention of CAD and stroke than tight glucose control, and reduces progression of nephropathy.

CV risk in diabetes is similar to that seen in patients with established CAD, at least after the disease has been present for several years. Because of their rapid progression of arterial disease, it is recommended that patients with diabetes receive aggressive preventive therapy with statins, aspirin, and inhibition of the renin-angiotensin system (see Table 5.5).

Table 5.5 Therapeutic recommendations for CV prevention in diabetes

Measure	Target
Aggressive lifestyle \pm oral hypoglycaemic therapy	HbA _{1c} $\leq 7\%$
Statin therapy (regardless of baseline lipid levels)	Cholesterol < 4.0 mmol/L, or $\downarrow > 25\%$ LDL < 2.0 mmol/L, or $\downarrow > 30\%$
Aggressive blood pressure control	$< 130 / < 80$ mmHg

ACE-I or ARB in most, especially if there is evidence of nephropathy.

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The metabolic syndrome and insulin resistance

The metabolic syndrome is a term describing a frequently observed cluster of adverse factors within an individual.

- It is characterized by:
 - visceral obesity
 - insulin resistance
 - moderate hypertension
 - dyslipidaemia (low HDL and high triglycerides with average cholesterol levels)
 - low-grade inflammation
- Several definitions of this syndrome have been proposed, but of these the American National Cholesterol Education Program—Adult Treatment Panel (NCEP ATP-III) diagnostic criteria (see Table 5.6) are the most practical and widely used, as well as being a robust predictor of vascular risk.
- The prevalence of this syndrome is increasing in parallel with the increase in numbers of obese and overweight individuals
- It has been described in a high proportion of American children and adolescents.
- It is projected to contribute substantially to the burden of atherosclerotic disease in society in the next few decades.

Table 5.6 ATP-III criteria for diagnosis of the metabolic syndrome

Variable	Threshold	
Waist circumference	>102 cm	(>40 in.) men
	>88 cm	(>35 in.) women
Fasting glucose	>6.1 mmol/L (11 mg/dL)	
Blood pressure	>130/>85 mmHg	
HDL cholesterol	<1 mmol/L	(40 mg/dL) men
	<1.3 mmol/L	(50 mg/dL) women
Triglycerides	>1.7 mmol/L (>150 mg/dL)	

≥3 out of 5 criteria must be satisfied for firm diagnosis.

Mechanisms of increased risk

Visceral obesity causes insulin resistance, leading to:

- increases in blood glucose
- adverse changes in blood lipids
- increased levels of inflammatory cytokines such as tumour necrosis factor alpha (TNF- α), causing endothelial dysfunction
- increases in vascular tone and BP
- local proatherosclerotic changes in the vascular wall.

Increased leptin and reduced adiponectin levels influence insulin sensitivity. Their incremental clinical value remains a subject of investigation. It has been proposed that the degree of insulin resistance is less important than the impact of other risk factors including lipids, BP, inflammation and pro-thrombotic factors, but these issues also remain under investigation.

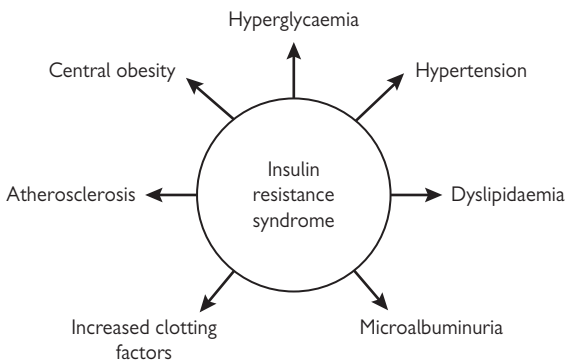


Fig. 5.8 Insulin resistance is an independent predictor of cardiovascular disease.¹⁻⁴.

- 1 Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP (1992). Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* **41**: 715-22.
- 2 Haffner SM, Miettinen H (1997). Insulin resistance implications for type II diabetes mellitus and coronary heart disease *Am J Med* **103**: 152-62.
- 3 Reaven GM (1994). Syndrome X: 6 years later. *J Int Med* **236**(suppl 736): 13-22.
- 4 Abuaisa B, Kumar S, Malik R, Boulton AJ. (1998). Relationship of elevated urinary albumin excretion to components of the metabolic syndrome in non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* **39**: 93-9.

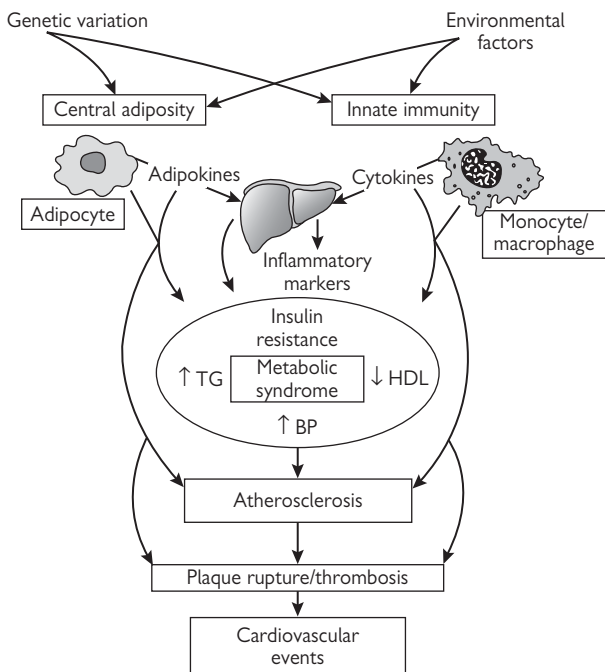


Fig. 5.9 Pathophysiology of atherosclerotic cardiovascular disease in the metabolic syndrome. Central adiposity and innate immunity play key roles in the development of insulin resistance, chronic inflammation, and metabolic syndrome features through the effects of adipokines (e.g. leptin, adiponectin, resistin) and cytokines (e.g. $\text{TNF-}\alpha$, interleukin-6) on liver, skeletal muscle, and immune cells. In addition, monocyte/macrophage-, and adipocyte-derived factors may have direct atherothrombotic effects that promote the development of atherosclerotic cardiovascular events. Common genetic variants and environmental factors may impact the development of atherosclerosis at multiple levels, through influences on central adiposity, innate immunity, glucose and lipoprotein metabolism, and vascular function. TG = triglycerides. Reproduced with permission from Reilly MP, Rader J (2003). The metabolic syndrome: more than the sum of its parts. *Circulation* **108**: 1546–51.

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Metabolic syndrome: management

Weight loss and exercise are the cornerstones of management of the metabolic syndrome. Management of insulin resistance with insulin-sensitizing drugs (metformin and thiazolidenediones) has theoretical benefits but is currently under investigation (see below). As far as management of the dyslipidaemia is concerned, treatment with statin is clearly indicated if 10-year CV risk is $\geq 20\%$, or if LDL-C is elevated (ATP-III recommend a threshold of >3.3 mmol/L). The nature of the risk-factor profile in the metabolic syndrome frequently results in the underestimation of 10-year risk, but at present no studies are currently available to support the use of specific evidence-based drug therapy in this syndrome.

Insulin sensitizers (thiazolidenediones, 'glitazones')

- The primary mode of action is to improve insulin sensitivity in muscle and adipose tissue (see Fig. 5.10).^{1,2}
- They are licensed as monotherapy, particularly in overweight patients with type 2 DM for whom metformin is not suitable.
- They are associated with modest weight gain.³
- They maintain lasting glycaemic control and, by targeting insulin resistance, improve a range of CV risk factors.⁴
- There may be a role for this class of drugs in the prevention of DM: the TRIPOD study enrolled 266 Hispanic women, in S California at high risk of developing DM, and randomized them to the thiazolidenedione, troglitazone, or placebo for 30 months. There was a 50% reduction in risk of developing DM with troglitazone use, and the benefits were sustained for >6 months after discontinuing the drug.⁵

1 Hällsten K, Virtanen KA, Lönnqvist F, et al (2002). Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. *Diabetes* **51**: 3479–85.

2 Virtanen KA, Hällsten K, Parkkola R, et al (2002). Different effects of rosiglitazone and metformin on adipose tissue glucose uptake in type 2 diabetes. *Diabetes* **51**(suppl. 2): A145. Abs 585-P.

3 Carey DG, Cowin GJ, Galloway GJ, et al (2002). Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients [corrected]. *Obes Res* **10**: 1008–15.

4 St John Sutton M, Rendell M, Dandona P, et al (2002). A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care* **25**: 2058–64.

5 Buchanan TA, Xiang AH, Peters RK, et al (2002). Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* **51**: 2796–803.

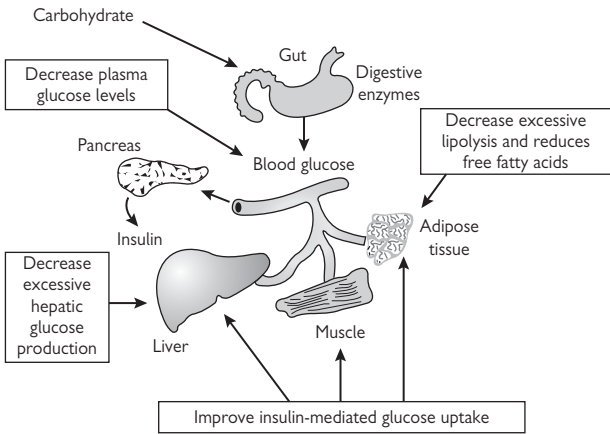


Fig. 5.10 Glitazones decrease insulin resistance at target tissues.

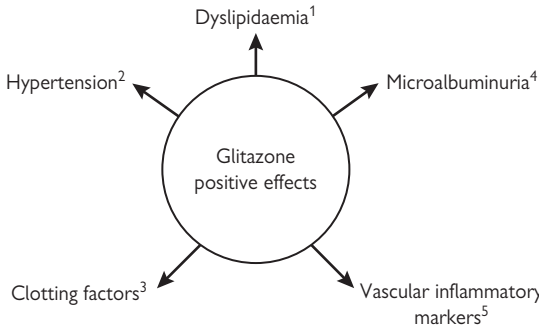


Fig. 5.11 Glitazones have positive effects on a range of cardiovascular risk factors.

- 1 Brunzell J *et al* (2001). *Diabetes* **50**(suppl 2): Abs 567-P.
- 2 Bakris GL, Dole JF, Porter LE, *et al* (2001). Rosiglitazone improves blood pressure in patients with type 2 diabetes mellitus. *Diabetes* **49**(suppl 1): A96, Abs 388.
- 3 Freed M *et al* (2000). *Diabetologia* **43**(suppl 1): Abs 1024.
- 4 Bakris GL, Weston WM, Rappaport EB, *et al* (1999). Rosiglitazone produces long-term reductions in urinary albumin excretion in type 2 diabetes (abstract). *Diabetologia* **42**(suppl 1): Abs 865 and poster.
- 5 Greenberg A, Haffner S, Weston W, *et al* (2001). Rosiglitazone reduces c-reactive protein, a marker of systematic inflammation, in type 2 diabetic patients. *Diabetologia* **44**(suppl 1): A222, Abs 853.

Angina pectoris

Angina pectoris refers to the pain caused by myocardial ischaemia. Ischaemia is usually caused by coronary stenosis due to atheroma but may be caused by tachycardia, anaemia, aortic stenosis, LVH of other aetiologies, syndrome X (chest pain with normal coronary arteries), and coronary artery spasm (Prinzmetal). These conditions may co-exist and will be exacerbated by physical exertion or emotional stress, which increase cardiac workload and energy requirement. Coronary artery spasm, in contrast, normally occurs at rest.

History and examination

- Angina pectoris is characterized by a deep and diffusely distributed central chest discomfort.
- Certain features of pain are of discriminative value. Patients will not be able to point to where the pain is coming from with one finger, but will use an open palm or fist over the centre or left parasternal aspect of their chest.
 - The pain is not sharp, (some patients confuse 'sharp' with 'severe').
 - Pain lasts longer than a few seconds and rarely exceeds an hour without varying in severity. Most episodes will last 1–5 minutes.
 - The response to glyceryl trinitrate (GTN), if there is one, will be almost immediate.
 - Responses that take more than 5 minutes are unlikely to be related to the drug.
- Chest wall tenderness suggests musculoskeletal pain and does not accompany angina.
- Dyspnoea, fatigue, nausea, and recurrent belching may also represent underlying ischaemia and can occur in the absence of the classical central chest pain. The clue to underlying ischaemic heart disease (IHD) lies in their precipitation by exertion or emotional stress.

Angina is often classified according to its temporal pattern and its relation to exertion because this loosely reflects prognosis.

- *Stable angina*—characterized by pain occurring after a relatively constant level of exertion.
- *Unstable angina*—characterized by pain on minor exertion or at rest, which is either new onset or a dramatic worsening of existing angina.
- *Crescendo angina*—characterized by pain on ever-diminishing levels of exertion, usually over a period of days.
- *Decubitus angina*—provoked by lying flat.

The *Canadian Cardiovascular Society (CCS)* system provides a quantitative means to describe exertional capacity and is divided into four classes:

- I. Minimal limitation of ordinary activity. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
- II. Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly; walking in cold, in wind, or under emotional stress.

- III. Marked limitation of ordinary physical activity; angina occurs on walking 50–100 m on level ground or climbing 1 flight of stairs at a normal pace in normal conditions.
- IV. Inability to perform any physical activity without discomfort; angina symptoms may be present at rest.

Physical examination

- This rarely reveals any direct evidence of IHD but will help with risk stratification and to exclude co-existing disease.
- Measure the pulse rate. This may be slowed by inferior ischaemia due to atrioventricular (AV) node ischaemia. A resting tachycardia, if present, usually represents activation of the sympathetic nervous system but may be due to an arrhythmia precipitated by ischaemia.
- BP measurement is essential to look for evidence of hypertension (predisposing to atheroma), or hypotension (may reflect cardiac dysfunction or over-medication).
- Precordial examination should include palpation for LVH, cardiac enlargement, or dyskinesis, and auscultation for added heart sounds (heart failure or acute ischaemia), aortic stenosis or mitral regurgitation (due to papillary muscle dysfunction).
- Examine for signs of heart failure by listening for fine, late-inspiratory crepitations at the lung bases, and looking for dependent pitting oedema (typically bilateral ankle \pm leg oedema, but sacral oedema may be the only manifestation if the patient has been recumbent for some time).
- Look for evidence of peripheral vascular disease by palpating for aortic aneurysm, feeling the carotid and limb pulses, listening for carotid, renal or femoral artery bruits, and assessing tissue integrity and capillary refill of the legs and feet.
- Examine for signs of hypercholesterolaemia: the eyes for xanthelasmata and corneal arcus, and the skin and tendons (especially the Achilles) for xanthomata.

Differential diagnosis

The differential diagnosis of anginal chest pain is wide and includes:

- anxiety and hyperventilation
- musculoskeletal chest wall pain
- cervical or thoracic root pain
- pneumothorax, pneumonia, or pulmonary embolus
- oesophageal problem (inflammation/spasm)
- other upper GI problem (gastritis, peptic ulcer, pancreatitis, cholecystitis)
- pericarditis
- aortic dissection
- mitral valve prolapse
- coronary emboli (LV mural thrombus, atrial myxoma).

Investigations

Further risk stratification will add to the diagnostic certainty achieved by history and examination. Measure full blood count (FBC), U&E, a full fasting lipid profile (total, LDL, and HDL cholesterol and triglyceride levels), and blood glucose. Chest X-ray (CXR) is not mandatory, but should be performed if there is suspicion of heart failure, a pulmonary condition, or an abnormality of the bony structures of the chest wall.

12-lead ECG

A resting ECG may not confirm the diagnosis but can point towards ischaemic heart disease. The presence of T-wave inversion (2 mm) or Q waves suggests previous myocardial injury. The presence of ST depression and, to a lesser extent, T-wave inversion during pain is a marker of ischaemia, and patients with these signs should be further investigated. If ST-segment deviation is observed at rest, an acute coronary syndrome must be excluded. 12-lead ECG can also help identify other causes of chest pain (LVH, arrhythmia, pericarditis).

Tests for inducible ischaemia

Tests such as exercise ECG, stress echocardiography (ECHO), or myocardial perfusion scanning are a useful adjunct to confirm the diagnosis and aid management.

Management

Lifestyle: Stop smoking. Encourage daily aerobic exercise within limits of exercise capacity. Look at occupational needs and advise adjustment if symptom level not compatible. Advise healthy diet, collaborating with dietitians if required.

Aspirin: (75 mg/24 h) In all cases unless active peptic ulcer disease or bleeding diathesis. Those with past peptic ulcer disease may take a gastro-protective agent such as a H₂ antagonist or proton pump inhibitor.

Anti-anginals: β -blockers: 1st line (e.g. atenolol 25–100 mg od or metoprolol 25–50 mg tds). Start on suspicion of IHD. Avoid only if contraindicated (asthma with confirmed β -agonist response (mortality improved in patients with angina and concomitant chronic obstructive pulmonary disease (COPD) if they can tolerate the reduced peak expiratory flow rate (PEFR)), uncontrolled severe LV dysfunction, bradycardia, coronary artery spasm).

Calcium antagonists: (e.g. amlodipine 5–10 mg od or diltiazem MR 90–180 mg bd) if β -blocker contraindicated.

Nitrates: (e.g. GTN spray) Used for control of breakthrough angina. Long-acting nitrates (e.g. isosorbide mononitrate MR 60–120 mg od) are a useful addition to β -blockers for prevention of attacks.

Statins: Reduce mortality by approximately one-third in all risk groups. However, the underlying risk of events must be taken into account when considering starting the drug because absolute risk reduction in young patients with low-risk IHD may be very small, with a possible harm of myositis, hepatic failure, and reduced compliance with other medications.

Chest pain clinics

Rapid-access or open-access chest pain clinics have transformed the primary and secondary care interface for UK patients since their incorporation into the National Service Framework. They have facilitated the shift of care of stable angina from generalist to specialist, and increased rates of angiography and revascularization. It is not known if this has an effect on mortality but it has certainly prioritized cardiac care and rates of diagnosis of IHD. The clinics usually involve a standardized referral form, which can be used by either a general practitioner (GP) or hospital physician.

The emphasis is on early exclusion of non-cardiac disease and risk stratification for IHD. Thus, in the first visit, the patient would see a specialist, perform an exercise test, and have baseline risk factors estimated. At the end of the consultation, the patient will be reassured that there is a low likelihood of IHD or will begin the path of treatment of risk factors and symptoms, ultimately leading to revascularization if required.

Acute coronary syndromes

Acute coronary syndrome (ACS) is an operational term used to describe a constellation of symptoms resulting from acute myocardial ischaemia. An ACS resulting in myocardial injury is termed myocardial infarction (MI). ACS includes the diagnosis of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). The term ACS is initially generally assigned by ancillary/triage personnel on initial contact with the patient. Guidelines for identification of ACS are summarized in Table 5.7 on [NSTEMI/UA: risk stratification](#), p. 295.

Definition

The current nomenclature divides ACS into two major groups, on the basis of delivered treatment modalities (see Fig. 5.12):

- **STEMI**—an ACS where patients present with chest discomfort and ST-segment elevation on ECG. This group of patients must undergo reperfusion therapy on presentation
- **NSTEMI and UA**—ACS where patients present with ischaemic chest discomfort associated with transient or permanent non-ST-elevation ischaemic ECG changes. If there is biochemical evidence of myocardial injury, the condition is termed NSTEMI, and in the absence of biochemical myocardial injury the condition is termed UA (see [Non-ST elevation myocardial infarction \(NSTEMI\)/unstable angina \(UA\)](#), p. 290). This group of patients is not treated with thrombolysis.

Initial management of ACS

- All patients with suspected ACS should be placed in an environment with continuous ECG monitoring and defibrillation capacity.
- The referring doctor should be instructed to give aspirin (300 mg PO if no contraindications) and *not* to give any IM injections (causes a rise in total creatine kinase (CK) and risk of bleeding with thrombolysis/anticoagulation).

Immediate assessment should include:

- rapid examination to exclude hypotension, note the presence of murmurs, and identify and treat acute pulmonary oedema
- secure intravenous (IV) access
- 12-lead ECG should be obtained and reported within 10 minutes.

Give:

- oxygen (initially only 28% if history of COPD)
- diamorphine 2.5–10 mg IV prn for pain relief
- metoclopramide 10 mg IV for nausea
- GTN spray 2 puffs/unless hypotensive

Take blood for:

- FBC/U&E—Supplement K^+ to keep it at 4–5 mmol/L
- glucose: may be \uparrow acutely post-MI, even in non-diabetic patients, and reflects a stress-catecholamine response and may resolve without treatment
- biochemical markers of cardiac injury (see [STEMI: diagnosis](#), p. 258).

- lipid profile—total cholesterol, LDL, HDL, triglycerides; serum cholesterol and HDL remain close to baseline for 24–48 hours but fall thereafter and take ≥ 8 weeks to return to baseline.
- Portable CXR will assess cardiac size and pulmonary oedema and exclude mediastinal enlargement.
- General examination should include peripheral pulses, fundoscopy, and abdominal examination for organomegaly and aortic aneurysm.

Conditions mimicking pain in ACS

- Pericarditis
- Dissecting aortic aneurysm
- Pulmonary embolism
- Oesophageal reflux, spasm or rupture
- Biliary tract disease
- Perforated peptic ulcer
- Pancreatitis

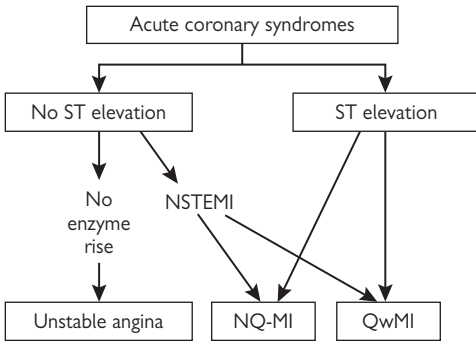


Fig. 5.12 Nomenclature of ACS: patients with ACS may present with or without ST elevation on the ECG. The majority of patients with ST elevation (large arrows) ultimately develop Q-wave MI (QwMI), whereas a minority (small arrow) develop a non-Q-wave MI (NQ-MI). Patients without ST-elevation are experiencing either UA or an NSTEMI, depending on the absence or presence of cardiac enzymes (e.g. troponin) detected in the blood. Adapted and reproduced with permission from Antman EM, Braunwald E (1997). Acute myocardial infarction. In Braunwald EB (ed). *Heart Disease: a textbook of cardiovascular medicine*. Philadelphia, PA WB Saunders.

ST elevation myocardial infarction (STEMI)

Patients with an ACS who have ST-segment elevation/left bundle branch block (LBBB) on their presenting ECG benefit significantly from immediate reperfusion, and are treated as one group under the term ST elevation myocardial infarction (STEMI).

Presentation



- *Chest pain* is usually similar in nature to angina, but of greater severity, longer duration and not relieved by sublingual GTN. Associated features include: nausea and vomiting, sweating, breathlessness, and extreme distress.
- The pains may be *atypical* (e.g. epigastric), or radiate to the back.
- Individuals with diabetes, or hypertension, and the elderly may suffer *painless* ('silent' infarcts) and/or *atypical infarction*. Presenting features include breathlessness from acute pulmonary oedema, syncope or coma from dysrhythmias, acute confusional states (mania/psychosis), diabetic hyperglycaemic crises, hypotension/cardiogenic shock, and central nervous system (CNS) manifestations resembling stroke, secondary to sudden reduction in cardiac output and peripheral embolization.

Management

Diagnosis is normally made on presentation, followed by rapid stabilization to ensure institution of reperfusion therapy without delay. This is in contrast to NSTEMI/UA where diagnosis may evolve over period of 24–72 hours (see [Non-ST elevation myocardial infarction \(NSTEMI\)/unstable angina \(UA\)](#), p. 290). The management principles of the various stages are outlined below and expanded subsequently.

- *Stabilizing measures* are generally similar for all ACS patients (see [STEMI: general measures](#), p. 262):
 - all patients with suspected STEMI should have continuous ECG monitoring in an area with full resuscitation facilities
 - patients should receive immediate aspirin 300 mg PO (if no contraindications), analgesia, and oxygen; secure IV access
 - rapid examination to exclude hypotension, note the presence of murmurs, and identify and treat acute pulmonary oedema. Right ventricular function (RVF) out of proportion to left ventricular function (LVF) suggests RV infarction (see [Right ventricular infarction](#), p. 272)
 - blood for FBC, biochemical profile, markers of cardiac injury, lipid profile, glucose, and portable CXR.
- *Diagnosis* must be made on the basis of history, ECG (ST elevation/new LBBB), and biochemical markers of myocardial injury. (NB: if ECG changes are diagnostic, reperfusion must not be delayed to wait for biochemical markers).

Treatment

- General medical measures (see  STEMI: general measures, p. 262).
- Reperfusion ((see  STEMI: reperfusion therapy (thrombolysis) and STEMI: reperfusion by primary PCI, p. 264–9).
- All patients with STEMI should be admitted to the coronary care unit (CCU).
- Discharge and risk prevention.

Factors associated with a poor prognosis

- Age >70 years
- Previous MI or chronic stable angina
- Anterior MI or right ventricular infarction
- LV failure at presentation
- Hypotension (and sinus tachycardia) at presentation
- Diabetes mellitus
- Mitral regurgitation (acute)
- Ventricular septal defect

STEMI: diagnosis

This is based on a combination of history, ECG, and biochemical markers of cardiac injury. In practice, history and ECG changes are normally diagnostic, resulting in immediate reperfusion/medical treatment. Biochemical markers of cardiac injury usually become available later and help to reconfirm the diagnosis, as well as to provide prognostic information (magnitude of rise).

ECG changes

- *ST segment elevation* occurs within minutes and may last for up to 2 weeks. ST elevation of ≥ 2 mm in adjacent chest leads and ≥ 1 mm in adjacent limb leads is necessary to fulfil thrombolysis criteria. Persisting ST elevation after 1 month suggests formation of LV aneurysm. The infarction site can be localized from ECG changes as indicated in the box opposite.
- *Pathological Q waves* indicate significant abnormal electrical conduction, but are not synonymous with irreversible myocardial damage. In the context of a 'transmural infarction', it may take hours or days to develop and usually remains indefinitely. In the standard leads, the Q wave should be $\geq 25\%$ of the R wave, 0.04 s in duration, with negative T waves. In the precordial leads, Q waves in V_4 should be >0.4 mV (4 small squares) and in V_6 >0.2 mV (2 small squares), in the absence of LBBB (QRS width <0.1 s or 3 small squares).
- *ST-segment depression (ischaemia at distance)* in a second territory (in patients with ST-segment elevation) is secondary to ischaemia in a territory other than the area of infarction (often indicative of multivessel disease), or reciprocal electrical phenomena. Overall, it implies a poorer prognosis.
- *PR-segment elevation/depression* and alterations in the contour of the P wave are generally indicative of atrial infarction. Most patients will also have abnormal atrial rhythms such as AF/flutter, wandering atrial pacemaker, and AV nodal rhythm.
- *T-wave inversion* may be immediate or delayed, and generally persists after the ST elevation has resolved.
- *Non-diagnostic changes*, but ones that may be ischaemic, include new LBBB or right bundle branch block (RBBB), tachyarrhythmias, transient tall peaked T waves or T-wave inversion, axis shift (extreme left or right), or AV block.

Biochemical markers of cardiac injury

Serial measurements evaluating a temporal rise and fall should be obtained to allow a more accurate diagnosis. CK and CK-MB from a skeletal muscle source tend to remain elevated for a greater time period in comparison to a cardiac source.

Conditions that may mimic ECG changes of a STEMI

- Left or right ventricular hypertrophy
- LBBB or left anterior fasciculate block
- Wolff–Parkinson–White syndrome
- Pericarditis or myocarditis
- Cardiomyopathy (hypertrophic or dilated)
- Trauma to myocardium
- Cardiac tumours (primary and metastatic)
- Pulmonary embolus
- Pneumothorax
- Intracranial haemorrhage
- Hyperkalaemia
- Cardiac sarcoid or amyloid
- Pancreatitis.

Localization of infarcts from ECG changes

<i>Anterior</i>	ST elevation and/or Q waves in V ₁ –V ₄ /V ₅
<i>Anteroseptal</i>	ST elevation and/or Q waves in V ₁ –V ₃
<i>Anterolateral</i>	ST elevation and/or Q waves in V ₁ –V ₆ and I and aVL
<i>Lateral</i>	ST elevation and/or Q waves in V ₅ –V ₆ and T-wave inversion/ST elevation/Q waves in I and aVL
<i>Inferolateral</i>	ST elevation and/or Q waves in II, III, aVF, and V ₅ –V ₆ (sometimes I and aVL)
<i>Inferior</i>	ST elevation and/or Q waves in II, III and aVF
<i>Inferoseptal</i>	ST elevation and/or Q waves in II, III, aVF, V ₁ –V ₃
<i>True posterior</i>	Tall R waves in V ₁ –V ₂ with ST depression in V ₁ –V ₃ ; T waves remain upright in V ₁ –V ₂ . This can be confirmed with an oesophageal lead if available (method similar to a nasogastric (NG) tube). Usually occurs in conjunction with an inferior or lateral infarct.
<i>RV infarction</i>	ST segment elevation in the right precordial leads (V _{3R} –V _{4R}). Usually found in conjunction with inferior infarction. This may only be present in the early hours of infarction.

Creatine kinase

- Levels twice the upper-limit of normal are taken as being abnormal.
- Serum levels rise within 4–8 hours post-STEMI and fall to normal within 3–4 days. The peak level occurs at about 24 hours but may be earlier (12 hours) and higher in patients who have had reperfusion (thrombolysis or PCI).

- False-positive rates of ~15% occur in patients with alcohol intoxication, muscle disease or trauma, vigorous exercise, convulsions, IM injections, hypothyroidism, pulmonary embolism (PE), and thoracic outlet syndrome.

CK-MB isoenzyme is more specific for myocardial disease. Levels may be elevated despite a normal total CK. However, CK-MB is also present in small quantities in other tissues (skeletal muscle, tongue, diaphragm, uterus, and prostate) and trauma or surgery may lead to false-positive results. If there is doubt about myocardial injury with CK-MB levels obtained, a cardiac troponin must be measured.

Cardiac troponins (TnT, TnI)

- Both TnT and TnI are highly sensitive and specific markers of cardiac injury.
- Serum levels start to rise by 3 hours post-MI, and elevation may persist up to 7–14 days. This is advantageous for diagnosis of late MI.
- In most STEMI cases, the diagnosis can be made using a combination of the clinical picture and serial CK/CK-MB levels. In the event of normal CK-MB levels and suspected non-cardiac sources of CK, troponins can be used.
- Troponins can also be elevated in non-ischaemic myocyte damage such as myocarditis, cardiomyopathy, and pericarditis.

Other markers

There are multiple other markers, but with increasing clinical availability of troponins, measurements are not recommended. These include aspartate transaminase (AST) (rise 18–36 hours post-MI) and lactate dehydrogenase (LDH) (rise 24–36 hours post-MI).

The time course of the various markers is shown in Fig. 5.13.

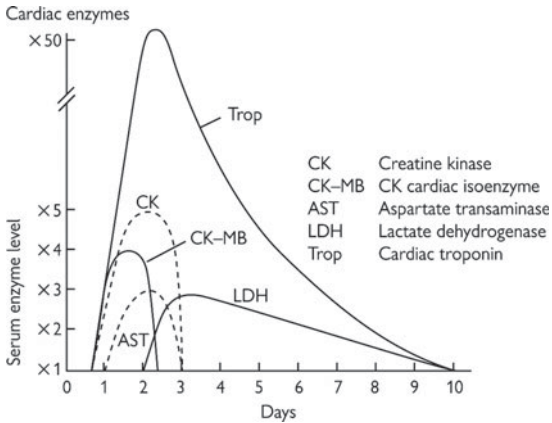


Fig. 5.13 Graph of the appearance of cardiac markers in the blood versus time of onset of symptoms. Adapted with permission from Wu AH et al. (1999). *Clin Chem* **45**: 1104–21.

Peak A: early release of myoglobin or CK-MB isoforms after AMI.


Peak B: cardiac troponin after AMI.

Peak C: CK-MB after AMI.

Peak D: Cardiac troponin after unstable angina.

Adapted with permission from Wu AH et al. (1999). *Clin Chem* **45**: 1104–21.

STEMI: general measures

1. Immediate stabilizing measures are as outlined on  Acute coronary syndromes, p. 254 for all ACS.
2. Control of cardiac pain:
 - *diamorphine* 2.5–10 mg IV is the drug of choice and may be repeated to ensure adequate pain relief, unless there is evidence of emerging toxicity (hypotension, respiratory depression). Nausea and vomiting should be treated with metoclopramide (10 mg IV) or a phenothiazine
 - *oxygen* to be administered at 2–5 L/min for at least 2–3 hours. Hypoxaemia is frequently seen post-MI due to ventilation–perfusion abnormalities secondary to LVF. In patients with refractory pulmonary oedema, continuous positive airways pressure (CPAP), or via formal endotracheal intubation may be necessary. Beware of CO₂ retention in patients with COPD
 - *nitrates* may lessen pain and can be given, providing the patient is not hypotensive (sublingual or intravenous). They need to be used cautiously in inferior STEMI, especially with RV infarction, as venodilation may impair RV filling and precipitate hypotension. Nitrate therapy has no effect on mortality (fourth International Study of Infarct Survival (ISIS-4)).
3. *Correction of electrolytes*: both low potassium and magnesium may be arrhythmogenic and must be supplemented, especially in the context of arrhythmias.
4. Strategies to limit infarct size (β -blockade, ACE-I and reperfusion).

β -blockade

- Early β -blockade in limiting infarct size and reducing mortality and early malignant arrhythmias. All patients (including primary PCI and thrombolysis patients) should have early β -blockade, but those with the following features will benefit most:
 - hyperdynamic state (sinus tachycardia, \uparrow BP)
 - ongoing or recurrent pain/reinfarction
 - tachyarrhythmias such as AF.
- *Absolute contraindications*: HR < 60 bpm, SBP < 100 mmHg, moderate to severe heart failure, AV conduction defect, severe airways disease.
- *Relative contraindications*: asthma, current use of calcium-channel blocker and/or β -blocker, severe peripheral vascular disease with critical limb ischaemia, large inferior MI involving the right ventricle.
- Use short-acting agent IV initially (metoprolol 1–2 mg at a time repeated at 1–2 minute intervals to a maximum dose of 15–20 mg) under continuous ECG and BP monitoring. Aim for a pulse rate of 60 bpm and SBP 100–110 mmHg. If haemodynamic stability continues 15–30 minutes after last IV dose, start metoprolol 50 mg tds. Esmolol is an ultra-short-acting IV β -blocker, which may be tried if there is concern whether the patient will tolerate β -blockers.

ACE inhibitors

After receiving aspirin, β -blockade (if appropriate), and reperfusion, all patients with STEMI/LBBB infarction should receive an ACE-I within the first 24 hours of presentation.

- Patients with high-risk/large infarcts, particularly with an anterior STEMI, a previous MI, elderly population, heart failure, and impaired LV function on imaging (ECHO) will benefit most.
- The effect of ACE-I appears to be a class effect: use the drug you are familiar with (e.g. ramipril 1.25 mg od).

STEMI: reperfusion therapy (thrombolysis)

Rapid reperfusion is the cornerstone of current management of STEMI and is marked by normalization of ST segments on ECG. Primary PCI and thrombolysis are the main reperfusion modalities. The best long-term outcome is achieved with primary PCI.

Reperfusion occurs in 50–70% of patients who receive thrombolysis within 4 hours of onset of pain (cf. ~20% of controls). As with primary PCI, thrombolysis also results in reduced mortality, LV dysfunction, heart failure, cardiogenic shock, and arrhythmias. However, the magnitude of the benefits obtained is smaller. Furthermore, patients must undergo cardiac catheterization to delineate their coronary anatomy before revascularization (achieved at the same time with primary PCI). Time is once again of paramount importance, and thrombolysis should be administered as soon as possible.

Indications for thrombolysis

- Typical history of cardiac pain within previous 12 hours and ST elevation in two contiguous ECG leads (>1 mm in limb leads or >2 mm in V₁–V₆).
- Cardiac pain with new/presumed new LBBB on ECG.
- If ECG is equivocal on arrival, repeat at 15–30 minute intervals to monitor progression.
- Thrombolysis should not be given if the ECG is normal, or there is isolated ST depression (must exclude true posterior infarct), or ST elevation with no preceding history of pain.

Timing of thrombolysis

- Greatest benefit is achieved with early thrombolysis (especially if given within 4 hours of onset of first pain).
- Patients presenting between 12 and 24 hours from onset of pain should be thrombolysed only with persisting symptoms and ST-segment elevation.
- Elderly patients (>65 years) presenting within the 12–24 hour time period with symptoms are best managed by primary PCI, as thrombolysis has demonstrated increased cardiac rupture.
- Patients presenting within 12–24 hours from onset of pain, whose clinical picture appears to have settled, should be managed initially as an NSTEMI, followed by early catheterization.

Choice of thrombolytic agent

- This is partly determined by local thrombolysis strategy.
- Allergic reactions and episodes of hypotension are greater with streptokinase (SK).
- Bolus agents are easier and quicker to administer, with a decrease in drug errors in comparison to first-generation infusions.


- Recombinant tissue plasminogen activator (rt-PA) has a greater reperfusion capacity and a marginally higher 30-day survival benefit than SK, but an increased risk of haemorrhage.
- More recent rt-PA derivatives have a higher 90-minute TIMI-III (Thrombolysis in Myocardial Infarction) flow rate, but similar 30-day mortality benefit to rt-PA.
- A rt-PA derivative should be considered for any patient with:
 - large anterior MI especially if within 4 hours of onset
 - previous SK therapy or recent streptococcal infection
 - hypotension (systolic BP <100 mmHg)
 - low risk of stroke (age <55 years, systolic BP <144 mmHg)
 - reinfarction during hospitalization where immediate PCI facilities are not available.

The characteristics of the major thrombolytic agents are on  p. 266.

Patients with greatest benefit from thrombolysis

- Anterior infarct
- Marked ST elevation
- Age >75 years
- Impaired LV function or LBBB, hypotensive
- Systolic BP <100 mmHg
- Patients presenting within 1 hour of onset of pain

Complications of thrombolysis

- Bleeding is seen in up to 10% of patients. Most bleeds are minor, at sites of vascular puncture. Local pressure is sufficient but occasionally transfusion may be required. In extreme cases, SK may be reversed by tranexamic acid (10 mg/kg slow IV infusion).
- Hypotension during the infusion is common with SK. Lay the patient supine and slow/stop infusion until the blood pressure rises. Treatment with cautious (100–500 mL) fluid challenges may be required, especially in inferior/RV infarction. Hypotension is not an allergic reaction and does not warrant treatment as such.
- Allergic reactions are common with SK and include a low-grade fever, rash, nausea, headaches, and flushing. Give hydrocortisone 100 mg IV with chlorphenamine 10 mg IV.
- Intracranial haemorrhage is seen in ~0.3% of patients treated with SK and ~0.6% with rt-PA.
- Reperfusion arrhythmias (most commonly a short, self-limiting run of idioventricular rhythm) may occur as the metabolites are washed out of the ischaemia tissue. See  Ventricular tachyarrhythmias post-MI, p. 284, for management.
- Systemic embolization may occur from lysis of thrombus within the left atrium, LV, or aortic aneurysm.

Absolute contraindications to thrombolysis

- Active internal bleeding
- Suspected aortic dissection

- Recent head trauma and/or intracranial neoplasm
- Previous haemorrhagic stroke at any time
- Previous ischaemic stroke within the past 1 year
- Previous allergic reaction to fibrinolytic agent
- Trauma and/or surgery within the past 2 weeks at risk of bleeding.

Relative contraindications to thrombolysis

- Trauma and/or surgery more than 2 weeks previously
- Severe uncontrolled hypertension (BP > 180/110 mmHg)
- Non-haemorrhagic stroke over 1 year ago
- Known bleeding diathesis, or current use of anticoagulation within therapeutic range (international normalized ratio (INR) 2 or over)
- Significant liver or renal dysfunction
- Prolonged (>10 min) cardiopulmonary resuscitation
- Prior exposure to SK (especially previous 6–9 months)
- Pregnancy or post partum
- Lumbar puncture within previous 1 month
- Menstrual bleeding or lactation
- History of chronic severe hypertension
- Non-compressible vascular punctures (e.g. subclavian central venous lines).

Doses and administration of thrombolytic agents

Streptokinase (SK)

- Give as 1.5 million units in 100 mL normal saline IV over 1 hour.
- There is no indication for routine heparinization after SK, as there is no clear mortality benefit and there is a small increase in risk of haemorrhage.

Recombinant tissue-type plasminogen activator (rt-PA, alteplase)

- The GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial suggested the 'front-loaded' or accelerated rt-PA (alteplase) is the most effective dosage regimen.
- Give 15 mg bolus IV then 0.75 mg/kg over 30 min (not to exceed 50 mg), then 0.5 mg/kg over 60 min (not to exceed 35 mg).
- This should be followed by IV heparin (see text).

Retepase

- Give two IV bolus doses of 10 units 10 minutes apart.

Tenecteplase

- Give as injection over 10 seconds at 30–50 mg according to body weight (500–600 mcg/kg).
- Maximum dose is 50 mg.

APSAC (anistreplase)

- Give as an IV bolus of 30 mg over 2–5 minutes.

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STEMI: reperfusion by primary PCI

Time is of the essence for reperfusion, and each institution should have its recommended protocol. It is imperative that there are no delays in either the decision-making or implementation processes for reperfusion. If primary PCI is chosen, one telephone call should ensure a rapid response.

Primary PCI

- Primary PCI is the current gold standard reperfusion strategy for treatment of STEMI.
- Primary PCI requires significant co-ordination between the emergency services, community hospitals, and invasive centres. It must only be performed if: (1) a primary PCI programme is available; (2) the patient presents to an invasive centre and can undergo catheterization without delay.

Indication for primary PCI

- All patients with chest pain and ST-segment elevation or new LBBB fulfil primary PCI criteria (compare with indications for thrombolysis).
- This will include a group of patients where ST-segment elevation may not fulfil thrombolysis criteria.
- In general, patients in whom thrombolysis is contraindicated should be managed by primary PCI. Cases where there is significant risk of bleeding must be managed individually.

Outcome in primary PCI


- Data from over 10 large randomized trials demonstrate a superior outcome in patients with STEMI who are treated with primary PCI in comparison to thrombolysis.
- There is a significant short-term, as well as long-term reduction in mortality and major adverse cardiac events (MACE) (death, non-fatal reinfarction and non-fatal stroke) in STEMI patients treated with primary PCI. Furthermore, primary PCI patients have overall better LV function, a higher vessel patency rate, and less recurrent myocardial ischaemia.
- Multiple studies (including PRAGUE-2 (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis) and DANAMI-2 (Danish Acute Myocardial Infarction)) have also demonstrated that interhospital transportation for primary PCI (community hospital to invasive centre) is safe, and primary PCI continues to remain superior to thrombolysis despite the time delays involved.

Complications

- Complications bleeding from the arterial puncture site, stroke, recurrent infarction, need for emergency CABG, and death, which are similar to high-risk PCI cases (~1%).
- The best results are obtained from high-volume centres with experience of primary PCI.

- Each primary PCI center will have its own policy for management of cases, including the use of low molecular weight heparin/unfractionated heparin (LMWH/UFH), antiplatelet agents (e.g. GPIIb/IIIa), etc. It is generally accepted that in the acute phase only the 'culprit' lesion(s)/vessel(s) will be treated. The pattern of disease in the remainder of the vessels will determine whether total revascularization should be performed as an inpatient or an elective case in the future.
- STEMI patients treated with primary PCI can be discharged safely within 72 hours of admission, without the need for further risk stratification.
- Primary PCI is more cost-effective in the long-term, with significant savings from fewer days in hospital, less need for readmission, and less heart failure.
- Post-discharge care, secondary prevention, and rehabilitation remain identical to other MI cases.

Rescue PCI

As an adjunct to thrombolysis, this should be reserved for patients who remain symptomatic post thrombolysis (failure to reperfuse), or develop cardiogenic shock (see  Cardiogenic shock, p. 288). We recommend all patients who do not settle post-thrombolysis (ongoing symptoms and ongoing ST-elevation with/without symptoms) to be discussed with the local cardiac centre, for urgent catheterization and revascularization.

Surgery for acute STEMI

Emergency surgical revascularization (CABG) cannot be widely applied to patients who suffer a MI outside of the hospital. CABG in uncomplicated STEMI patients after 6 hours from presentation is contraindicated, secondary to significant haemorrhage into areas of infarction. Unstable patients have a very high perioperative mortality.

CABG in the context of an acute STEMI is of value in the following situations:

- persistent or recurrent chest pain despite thrombolysis/primary PCI
- high-risk coronary anatomy on catheterization (left main stem coronary artery (LMS), left anterior descending coronary artery (LAD) ostial disease)
- complicated STEMI (acute MR, ventricular septal defect (VSD))
- patients who have undergone successful thrombolysis but with surgical coronary anatomy on catheterization
- patients known to have surgical coronary anatomy on catheterization performed prior to admission with STEMI.

STEMI: additional measures

Low molecular weight and unfractionated heparin

UFH

- There is no indication for 'routine' IV heparin following SK.
- IV heparin (4000 U max IV bolus followed by 1000 U/h max adjusted for an aPTT (activated partial thromboplastin time) ratio of 1.5–2.0 times control) should be used routinely following rt-PA and its derivatives for 24–48 hours.

LMWH

- There are trial data for the use of LMWH and thrombolysis (e.g. enoxaparin 30 mg IV bolus, then 1 mg/kg SC q12h).
- LMWH can be used at a prophylactic dose to prevent thromboembolic events in patients who are slow to mobilize, as an alternative to UFH.

Clopidogrel

- Should be administered to all patients undergoing primary PCI (loading dose 300 mg PO followed by 75 mg od).
- If coronary stents are used, patients should remain on clopidogrel for at least 1 month in bare-metal stents and 12 months in coated stents.
- More data are required to see whether longer-term treatment may be of benefit following thrombolysis alone.

Glycoprotein IIb/IIIa inhibitors

- There are multiple ongoing trials to evaluate their role in combination with thrombolysis and/or LMWH.
- Are recommended routinely in the context of STEMI patients treated with primary PCI. Lower doses of LMWH/UFH should be used (consult manufacturer's information sheet for individual agents).
- They can also be used in the context of rescue PCI subsequent to failed thrombolysis, although there is a greater risk of bleeding. Each case must be judged on its merits.

Magnesium

- Earlier trials giving Mg^{2+} before or with thrombolytic agents showed some benefit in mortality. ISIS-4 showed no benefit from the routine use of IV magnesium post-MI. However Mg^{2+} was given late (6 hours) after thrombolysis, by which time the protective effect of Mg^{2+} on reperfusion injury may have been lost. Trials are ongoing.
- Current accepted role for Mg^{2+} is confined to Mg^{2+} deplete patients and patients with reperfusion, supraventricular, and ventricular arrhythmias.
- Dose: 8 mmol in 20 mL 5% dextrose over 20 minutes followed by 65 mmol in 100 mL 5% dextrose over 24 hours. (Contraindications: serum $Cr > 0.0 \mu\text{mol/L}$, 3° AV block.)

Calcium antagonists

- Best avoided, especially in the presence of LV impairment.
- Diltiazem and verapamil started after day 4–5 in post-MI patients with normal LV function have a small beneficial effect.
- Amlodipine is safe to be used in patients with poor LV post-MI.
- Nifedipine has been shown to increase mortality and should be avoided.

Right ventricular infarction

- RV infarction results in elevated right-sided pressures (RA, right ventricular end-diastolic pressure (RVEDP)) and low left-sided pressures (BP, CO).
- It is common in inferior STEMI.

Diagnosis

- *Clinical*: signs of right heart failure (↑JVP (jugular venous pressure), Kussmaul's sign, pulsus paradoxus) with absence of pulmonary oedema in the context of a low-output state (↓BP, cold peripheries).
- *ECG*: in patients with inferior STEMI, a 0.1 mV (>1 mm) ST segment elevation in any one of leads V_{4R} – V_{6R} is highly sensitive and specific for RV infarction. See Fig. 5.14 for different ECG patterns identified in right-sided precordial leads. Changes may be transient and present in the early stages only.
- *ECHO*: looking for RV dilation and wall motion abnormalities.

Management

- Aim to maintain a high RV preload:
 - initially give 1–2 L of colloid rapidly
 - avoid use of nitrates and diuretics as they reduce pre-load and can worsen hypotension
 - in patients requiring pacing, AV synchrony must be maintained to ensure maximal CO (atrial and ventricular wires)
 - cardiovert any arrhythmias (supraventricular tachycardia (SVT), AF/flutter or ventricular rhythms).
- Reduce afterload:
 - this is particularly important if there is concomitant LV dysfunction
 - insert intra-aortic balloon pump (IABP)
 - arterial vasodilators can be used with caution (Na nitroprusside, hydralazine), or ACE-Is.
- Inotropic support should ideally be avoided and used if all other measures fail to restore haemodynamic status.
- Reperfusion of the right coronary artery (RCA) (PCI and thrombolysis) has been demonstrated to improve RV function and reduce mortality.

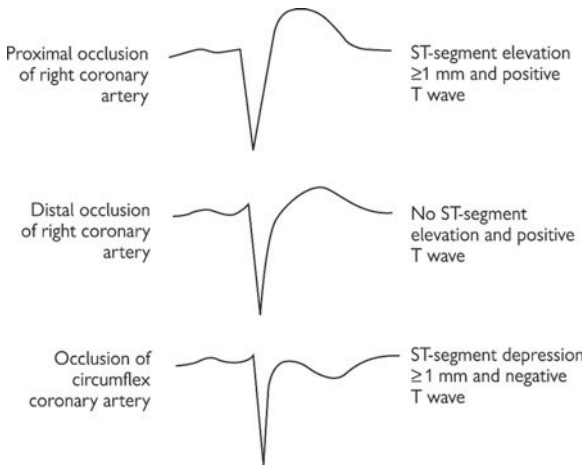


Fig. 5.14 ST-elevation and T-wave configuration in lead V_{4R} in inferoposterior AMI. Proximal occlusion of the RCA produces ST elevation >1 mm and a positive T wave. Distal occlusion is characterized by a positive T wave but no ST elevation. Occlusion of the circumflex artery produces a negative T wave and ST depression of at least 1 mm. Adapted with permission from Wellens HJ (1999). *N Engl J Med* 340: 1383.

STEMI: pre-discharge risk stratification

It is important to identify the subgroup of patients who have a high risk of reinfarction or sudden death. They should undergo coronary angiography with view to revascularization prior to discharge (if not treated with primary PCI) and/or electrophysiological investigations as necessary.

Primary PCI group

- STEMI patients treated with primary PCI are at a much lower risk of developing post-MI complications.
- There is ongoing debate whether patients treated with primary PCI should have total revascularization as an inpatient or whether this can be achieved after functional testing on an outpatient basis. Follow your local policy.
- Patients who should have electrophysiological assessment prior to discharge are listed below.

Thrombolysis group

- Patients treated with thrombolysis should be risk stratified prior to discharge, and high-risk patients should have inpatient (or early outpatient) angiography. High-risk patients include:
 - significant post-infarct angina or unstable angina
 - positive exercise test (modified Bruce protocol) with angina, >1 mm ST depression or fall in BP
 - cardiomegaly on CXR, poor LV function on ECHO (ejection fraction (EF) <40%)
 - documented episodes of regular venous embolisms (VEs) and VT 24 h post infarction
 - frequent episodes of silent ischaemia on Holter monitoring.

Electrophysiological study

All STEMI patients with (1) non-sustained VT and documented EF <40% or (2) sustained/pulseless ventricular tachycardia/fibrillation (VT/VF) (regardless of EF) should undergo electrophysiological testing prior to discharge (MADIT (Multicenter Automatic Defibrillator Implantation trial) and MUSTT (Multicenter Unsustained Tachycardia Trial) trials), with a view to defibrillator implantation.

Discharge and secondary prevention

- *Length of hospital stay in uncomplicated patients:* the thrombolysis group need to undergo risk stratification prior to discharge and tend to have a mean hospital stay of 5–7 days. The primary PCI group have shorter hospital stay, between 3–4 days.
- Prior to discharge, an agreed plan between the patient (patient's family) and physician is necessary to address modifiable risk factors, beneficial medication, and a rehabilitation programme.
- Modifiable risk factors include:
 - management of lipids and use of statins
 - detection and treatment of diabetes
 - ensuring blood pressure is adequately controlled
 - counselling to discontinue smoking
 - advice on a healthy diet and weight loss.

- It is vital patients understand the medical regime, and in particular the importance of long-term 'prognostic medication'. Unless there are contraindications, all patients should be on a minimum of:
 - aspirin 75 mg od (if true allergy, use clopidogrel 75 mg od)
 - ACE-I at the recommended dosage
 - statin at the recommended dosage
- The role of long term formal anticoagulation is controversial.
- All patients must be plugged into a rehabilitation programme.

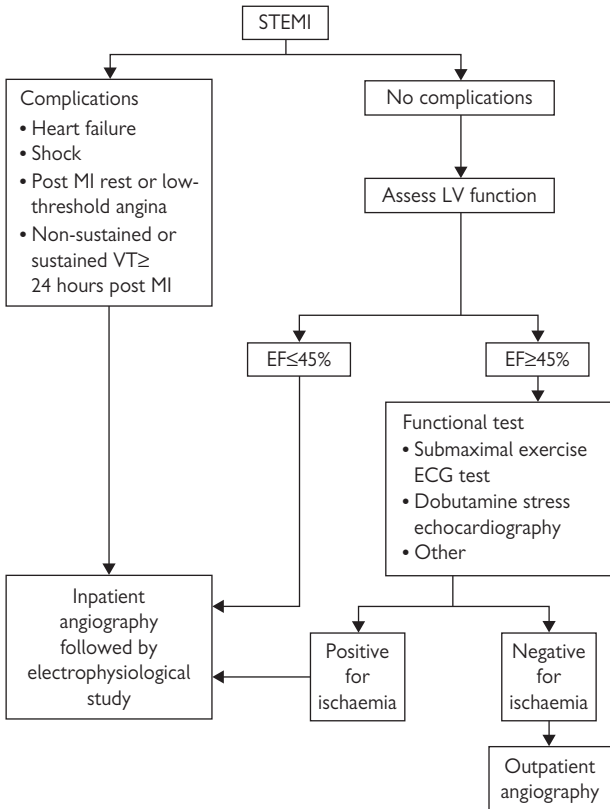


Fig. 5.15 Suggested strategy post-STEMI in patients who have undergone thrombolysis to determine the need for inpatient angiography/electrophysiological study. Adapted from Antman EM (2000). *Cardiovascular Therapeutics* 2nd edition. Saunders, Philadelphia.

STEMI: complications

Complications


These include:

- continuing chest pain
- fever
- a new systolic murmur—VSD, acute MR, or pericarditis
- dysrhythmia (VT, AV block ectopics, and bradycardia)
- pump failure—hypotension, cardiac failure, and cardiogenic shock.

Complications are encountered more commonly in patients post-STEMI, but can also be found in NSTEMI patients. In NSTEMI patients, complications are more common where multiple cardiac events have occurred.

Further chest pain

- Chest pain post-MI is not necessarily angina. Careful history is needed to characterize pain. If there is doubt about the aetiology of pain in the absence of ECG changes, stress/thallium imaging may aid diagnosis.
- A bruised sensation and musculoskeletal pains are common in the first 24–48 hours, especially in patients who have received cardiopulmonary resuscitation (CPR) or repeated DC shock. Use topical agents for skin burns.
- *Recurrent infarction* is an umbrella term including both extension of infarction in the original territory, or repeated infarct in a second territory:
 - usually associated with recurrent ST elevation
 - if cardiac enzymes are not yet back to normal, a significant change is a twofold rise above the previous nadir
 - patients should ideally undergo immediate PCI. Thrombolysis is an alternative, but a less attractive approach. Standard thrombolysis criteria must be met. Bleeding is a risk (NB: SK should not be used on a second occasion).
- *Post-infarction angina* (angina developing within 10 days of MI) should be treated with standard medical therapy. All patients with angina prior to discharge should undergo cardiac catheterization and revascularization as an inpatient.
- *Pericarditis* presents as sharp, pleuritic, and positional chest pain, usually 1–3 days post infarct. It is more common with STEMI. A pericardial friction rub may be audible. ECG changes are rarely seen. Treat with high-dose aspirin (600 mg qds PO) covering with a proton pump inhibitor (e.g. lansoprazole 30 mg od PO). Other NSAIDs have been associated with higher incidence of LV rupture and increased coronary vascular resistance, and are probably best avoided.
- *Pericardial effusion* is more common with anterior MI, especially if complicated by cardiac failure. Tamponade is rare and the result of ventricular rupture and/or haemorrhagic effusions. Detection is with a combination of clinical features and echocardiography. Most resolve gradually over a few months with no active intervention.

- *Pulmonary thromboembolism* can occur in patients with heart failure and prolonged bed rest. Routine use of prophylactic LMWH and UFH combined with early mobilization have reduced the incidence of PE. Sources include lower limb veins and/or RV (see  Pulmonary embolism: assessment, p. 742).

Fever

- Often seen and peaks 3–4 days post-MI
- Associated with elevated white cell count (WCC) and raised CRP
- Other causes of fever should be considered (infection, thrombophlebitis, venous thrombosis, drug reaction, pericarditis).

Ventricular septal defect post-MI

- Classically seen 24 hours (highest risk) to 10 days post-MI and affects 2–4% of cases.
- *Clinical features* include rapid deterioration with a harsh pansystolic murmur (maximal at the lower left sternal edge), poor perfusion, and pulmonary oedema. The absence of a murmur in the context of a low output state does not rule out a VSD.
- *Diagnosis:*
 - echocardiography—the defect may be visualized on 2D ECHO, and colour flow Doppler shows the presence of left-to-right shunt. Anterior infarction is associated with apical VSD, and inferior MI with basal VSD. Failure to demonstrate a shunt on ECHO does not exclude a VSD.
 - Pulmonary artery (PA) catheter (especially in absence of ECHO or inconclusive ECHO results)—a step-up in oxygen saturation from RA to RV confirms the presence of a shunt, which may be calculated by:

$$Q_p : Q_s = \frac{(\text{Art sat} - \text{RA sat})}{(\text{Art sat} - \text{PA sat})} \text{ where } \frac{Q_p}{Q_s} = \frac{\text{pulmonary blood flow}}{\text{systemic blood flow}}$$

and Art = arterial and sat = saturation

Management

Stabilization measures are all temporizing until definitive repair can take place. Hypotension and pulmonary oedema should be managed as described elsewhere. Important principles are:

- invasive monitoring (PA catheter and arterial line) to dictate haemodynamic management. RA and PCWP dictate fluid administration or diuretic use. CO, mean arterial pressure, and arterial resistance determine the need for vasodilator therapy.
- if SBP > 100 mmHg, cautious use of vasodilator therapy, generally with nitroprusside, will lower the systemic vascular resistance and reduce the magnitude of the shunt. Nitrates will cause venodilatation and increase the shunt and should be avoided. Not be used with renal impairment.
- inotropes if severely hypotensive (initially dobutamine but adrenaline may be required depending on haemodynamic response). Increasing systemic pressure will worsen shunt.
- in most cases an intra-aortic balloon should be inserted rapidly for counter pulsation.
- liaise with surgeons early for possible repair. Operative mortality is high (20–70%), especially in the context of perioperative shock, inferoposterior MI, and RV infarction. Current recommendations are for high-risk early surgical repair combined with CABG ± mitral valve (MV) repair/replacement.

- if the patient has been weaned off pharmacological and/or mechanical support, it may be possible to postpone surgery for 2–4 weeks to allow for some level of infarct healing.
- patients should ideally undergo catheterization prior to surgical repair to ensure culprit vessel(s) are grafted.
- closure of the VSD with catheter placement of an umbrella-shaped device has been reported to stabilize critically ill patients until definitive repair is possible.



Acute mitral regurgitation post-MI

- MR due to ischaemic papillary muscle dysfunction or partial rupture is seen 2–10 days post-MI. Complete rupture causes torrential MR and is usually fatal.
- More commonly associated with inferior MI (posteromedial papillary muscle) than anterior MI (anterolateral papillary muscle).
- ‘Silent MR’ is quite frequent and must be suspected in any post-MI patient with unexplained haemodynamic deterioration.
- Diagnosis is by ECHO. In severe MR, PA catheterization will show a raised pressure with a large v wave.

Management (see  Acute mitral regurgitation, p. 736).

- Treatment with vasodilators, generally nitroprusside, should be started as early as possible once haemodynamic monitoring is available.
- Mechanical ventilation may be necessary.
- Liaise with surgeons early for possible repair.

Pseudoaneurysm and free-wall rupture

- Demonstrated in up to 6% of STEMI patients and leads to sudden death in two thirds.
- A proportion present subacutely with cardiogenic shock allowing time for intervention (see  Cardiogenic shock, p. 288).
- Diagnosis of subacute cases can be made on a combination of clinical features of pericardial effusion, tamponade, and echocardiography.
- Patients who have undergone early thrombolysis have a lower chance of wall rupture.
- Stabilization of the patient follows similar lines to cardiogenic shock (see  Cardiogenic shock, p. 288). The case must be discussed with surgeons immediately, with a view to repair.

Cocaine-induced MI

- The incidence of cocaine-induced MI, LV dysfunction, and arrhythmias is on the increase.
- It has been estimated that 14–25% of young patients presenting to urban emergency departments with non-traumatic chest pain may have detectable levels of cocaine and its metabolites in their circulation. Of this group, 6% have enzymatic evidence of MI (figures are from USA).
- Most patients are young, non-white, male, cigarette smokers without other risk factors for ischaemic heart disease.

Diagnosis

- Can be difficult and must be suspected in any young individual with chest discomfort at low risk of developing ischaemic heart disease.
- *Chest pain*: occurs most commonly within 12 h of cocaine use. Effects can return up to 24–36 h later, secondary to long-lasting active metabolites.
- *ECG*: is abnormal with multiple non-specific repolarization changes in up to 80% of cases, and approximately 40% may have diagnostic changes of STEMI qualifying for reperfusion therapy (see [ECG](#) STEMI: diagnosis, p. 258).
- *Biochemical markers of cardiac injury*: can be misleading, as most patients will have elevated CK levels secondary to rhabdomyolysis. TnT and TnI are vital to confirm myocardial injury.

Management

General measures

- These are the same as for anyone presenting with an MI: oxygen, high flow 5–10 L unless there is a contraindication; analgesia; aspirin 75 mg od.
- GTN: to be given at high doses as IV infusion (>10 mg/h final levels) and dose titrated to symptoms and haemodynamic response (see [ECG](#) ST elevation myocardial infarction (STEMI), p. 256).
- Benzodiazepines: to reduce anxiety.

Second-line agents

- *Verapamil*: is given in high doses and has the dual function of reducing cardiac work load and hence restoring oxygen supply and demand, as well as reversing coronary vasoconstriction. Should be given cautiously as 1–2 mg IV bolus at a time (up to 10 mg total) with continuous haemodynamic monitoring. This should be followed by high-dose oral preparation to cover the 24 hour period for at least 72 hours post last dose of cocaine (80–120 mg PO tds).
- *Phentolamine*: is an α -adrenergic antagonist and readily reverses cocaine-induced vasoconstriction (2–5 mg IV and repeated if necessary). It can be used in conjunction with verapamil.
- *Labetalol*: has both α - and β -adrenergic activity and can be used after verapamil and phentolamine if the patient remains hypertensive. It is effective in lowering cocaine-induced hypertension, but has no effect on coronary vasoconstriction.




- *Reperfusion therapy*: evidence for use of thrombolysis is limited and generally associated with poor outcome secondary to hypertension-induced haemorrhagic complications. If the patient fails to settle after implementing first-line measures, verapamil, and phentolamine, they should undergo immediate coronary angiography followed by PCI if appropriate (evidence of thrombus/vessel occlusion). In the event that angiography is not available, thrombolytic therapy can be considered.
- **CAUTION**: β -blockers must be avoided (e.g. propranolol). They exacerbate coronary vasoconstriction by allowing unopposed action of the α -adrenergic receptors.

Teaching points: cocaine-induced MI

Pathogenesis

- The cause of myocardial injury is multifactorial, including an increase in oxygen demand (\uparrow HR, \uparrow BP, \uparrow contractility) in the context of decrease in supply caused by a combination of inappropriate vasoconstriction (in areas of minor atheroma), enhanced platelet aggregation, and thrombus formation.
- The effects can be delayed, as the metabolites of cocaine are potent active vasoconstrictors and can remain in the circulation for up to 36 hours (or longer), resulting in a recurrent wave of symptoms.

Other complications

- *Cocaine-induced myocardial dysfunction* is multifactorial and includes MI, chronic damage secondary to repetitive sympathetic stimulation (as in pheochromocytoma), myocarditis secondary to cocaine impurities/infection, and unfavourable changes in myocardial/endothelial gene expression.
- *Cocaine-induced dysrhythmias* include both atrial and ventricular tachyarrhythmias, as well as asystole and heart block (see post-MI arrhythmias (see  Ventricular tachyarrhythmias post-MI; Atrial tachyarrhythmia post-MI; Bradyarrhythmias and indications for pacing; Bradyarrhythmias post-MI, pp. 284–5). and cardiopulmonary resuscitation (see  Adult advanced life support, p. 712).
- *Aortic dissection* (see  Aortic dissection: assessment, p. 766).

Ventricular tachyarrhythmias post-MI

Accelerated idioventricular rhythm

- Common (up to 20%) in patients with early reperfusion in first 48 h.
- Usually self-limiting and short lasting with no haemodynamic effects.
- If symptomatic, accelerating sinus rate with atrial pacing or atropine may be of value. Suppressive anti-arrhythmic therapy (lidocaine, amiodarone) is only recommended with degeneration into malignant ventricular tachyarrhythmias.

Ventricular premature beats (VPB)

- Common and not related to incidence of sustained VT/VF.
- Generally treated conservatively with the aim to correct acid–base and electrolyte abnormalities (aim $K^+ > 4.0$ mmol/L and $Mg^{2+} > 1.0$ mmol/L).
- Peri-infarction β -blockade reduces VPB.


Non-sustained and monomorphic ventricular tachycardia

- Associated with a worse clinical outcome.
- Correct reversible features such as electrolyte abnormalities and acid–base balance.
- DC cardioversion for haemodynamic instability.
- Non-sustained VT and haemodynamically stable VT (slow HR < 100 bpm) can be treated with amiodarone (300 mg bolus IV over 30 min, followed by 1.2 g infusion over 24 h). Lidocaine is no longer recommended as first line. Procainamide is an effective alternative, but is arrhythmogenic.
- For incessant VT on amiodarone consider overdrive pacing.

Ventricular fibrillation and polymorphic VT

- A medical emergency and requires immediate defibrillation.
- In refractory VF consider vasopressin 40 U IV bolus.
- Amiodarone 300 mg IV bolus to be continued as an infusion (see above) if output restored.

Atrial tachyarrhythmias post-MI

- Includes SVT, AF, and atrial flutter.
- If patient is haemodynamically unstable they must undergo immediate synchronized DC cardioversion.
- Haemodynamically stable patients can be treated with digoxin, β -blockers, and/or calcium-channel blockers (see  Treatment options in tachyarrhythmias, p. 721).
- Amiodarone can be used to restore sinus rhythm. However, it is not very effective in controlling rate. Class I agents should generally be avoided as they increase mortality.
- In AF and flutter, patients should undergo anticoagulation to reduce embolic complications if there are no contraindications.

Bradyarrhythmias and indications for pacing

Alternating or isolated RBBB/LBBB do not need pacing (unless haemodynamically unstable or progression to higher levels of block). New bifascicular block (RBBB with either LAD or RAD) or BBB with first-degree AV block may require prophylactic pacing depending on the clinical picture. Indications for pacing should not delay reperfusion therapy. Venous access (femoral or internal jugular vein) should be obtained first, and a pacing wire inserted later. External temporary cardiac pacing, atropine (300 mcg to 3 mg IV bolus) and isoprenaline can be used to buy time.

Bradyarrhythmias post-MI

First-degree AV block

- Common and no treatment required.
- Significant PR prolongation (>0.20 s) is a contraindication to β -blockade.

Second-degree AV block

This indicates a large infarction affecting conducting systems, and mortality is generally increased in this group of patients.

- *Mobitz type I* is self-limiting with no symptoms. Generally, requires no specific treatment. If symptomatic or there is progression to complete heart block, will need temporary pacing.
- *Mobitz type II*, 2:1, 3:1 should be treated with temporary pacing, regardless of whether it progresses to complete heart block.

Third-degree AV block

- In the context of an inferior MI, can be transient and does not require temporary pacing unless there is haemodynamic instability or an escape rhythm of <40 bpm.
- Temporary pacing is required with anterior MI and unstable inferior MI.

Hypotension and shock post-MI

(See  Cardiogenic shock, p. 288).


The important principles in managing hypotensive patients with MI are:


- if the patient is well perfused peripherally, no pharmacological intervention is required
- try to correct any arrhythmia, hypoxia, or acidosis
- arrange for an urgent ECHO to exclude a mechanical cause for hypotension (e.g. mitral regurgitation, VSD, ventricular aneurysm) that may require urgent surgery.

Subgroups

Patients may be divided into two subgroups.

1. Hypotension with pulmonary oedema

- Secure central venous access—internal jugular lines are preferable if the patient may have received thrombolytic therapy.
- Commence *inotropes* (See  Cardiogenic shock, p. 288).
- Further invasive haemodynamic monitoring as available (PA pressures and wedge pressure monitoring, arterial line).
- Ensure optimal filling pressures, guided by physical signs and PA diastolic or wedge pressure. Significant mitral regurgitation will produce large v waves on the wedge trace and give high estimates of LVEDP.
- Ensure rapid coronary reperfusion (if not already done), with either thrombolytic therapy or primary PCI where available.

Intra-aortic balloon counter pulsation (See  Intra-aortic balloon counterpulsation, p. 822) may allow stabilization until PCI can be performed.


2. Hypotension without pulmonary oedema

- This may be due to either RV infarction or hypovolaemia.

Diagnosis

- Check the JVP and right atrial pressure. This will be low in hypovolaemia and high in RV infarction.
- RV infarction on ECG is seen in the setting of inferior MI and ST elevation in right-sided chest leads (V_{3R}–V_{4R}).

Management

- In either case, cardiac output will be improved by cautious plasma expansion. Give 100–200 mL of colloid over 10 minutes and reassess.
- Repeat once if there is some improvement in blood pressure and the patient has not developed pulmonary oedema.
- Invasive haemodynamic monitoring with a PA catheter (Swan–Ganz) is necessary to ensure hypotension is not due to low left-sided filling pressures. Aim to keep PCWP 12–15 mmHg.
- Start *inotropes* if BP remains low despite adequate filling pressures.
- Use IV nitrates and diuretics with caution, as venodilatation will compromise RV and LV filling and exacerbate hypotension.
- See  p.272 for management of RV infarction.

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Cardiogenic shock

- Affects 5–20% of patients, and up to 15% of MI patients can present with cardiogenic shock.
- Management involves a complex interaction between many medical, surgical, and intensive care teams, with multiple invasive and non-invasive measures. Despite significant advances, prognosis remains poor.
- Therefore, the absolute wishes of the patient with regard to such an invasive strategy should be respected from the onset.

Diagnosis

A combination of clinical and physiological measures:

- *clinical*: marked, persistent (>30 min) hypotension with SBP < 80–90 mmHg
- *physiological*: low cardiac index (<1.8 L/mm/m²) with elevated LV filling pressure (PCWP > 18 mmHg).

Management

- Complex and must be quick.
- Correct reversible factors, including:
 - arrhythmias and aim to restore sinus rhythm
 - acid–base and electrolyte abnormalities
 - ventilation abnormalities—intubate if necessary
- Rapid haemodynamic, echocardiographic, and angiographic evaluation:
 - *haemodynamic*: to ensure adequate monitoring and access, including central venous lines, Swan–Ganz, arterial line insertion, urinary catheter
 - *echocardiographic*: to assess ventricular systolic function and exclude mechanical lesions, which may need to be dealt with, emergency cardiac surgery including mitral regurgitation (NB: tall v waves on PCWP trace), VSD, and ventricular aneurysm/pseudoaneurysm.
 - *angiographic*: with a view to PCI or CABG if appropriate
- Aim to improve haemodynamic status achieving a SBP ≥ 90 mmHg guided by physical signs and LV filling pressures. As a general guide:
 - PCWP < 15 mmHg—cautious of IV fluids (colloids) in 100–200 mL aliquots
 - PCWP > 15 mmHg—inotropic support ± diuretics (if pulmonary oedema).
- Inotropes should be avoided if at all possible in acutely ischaemic patients. The aim should be to rapidly restore/maximize coronary flow and offload LV. Early revascularization is vital and has been shown to decrease mortality. IABP will partially help achieve the aforementioned goals.
- If haemodynamic status does not improve post revascularization and IABP insertion, inotropes should be used. The choice of agent can be difficult and should partly be guided by local protocols and expertise. Generally accepted choices depend on the clinical picture and include:
 - if patient is hypotensive (± pulmonary oedema)—start with dopamine (up to 15 mcg/kg/min) and if ineffective substitute to adrenaline (epinephrine) and/or noradrenaline (norepinephrine)

- if the patient has adequate blood pressure (\pm pulmonary oedema)—dobutamine to increase cardiac output (starting at 2.5–5 mcg/kg/min and increasing to 20 mcg/kg/min) titrating to HR and haemodynamics. Phosphodiesterase inhibitors can be used as an alternative. If hypotension and tachycardia complicate dobutamine/PDI inhibitor treatment, (nor)adrenaline can be added as a second agent to achieve desired haemodynamic effect.
- Use of diuretics, thrombolysis, GPIIb/IIIa antagonists, LMWH/UFH should follow normal principles, and is based on the clinical picture.

Non-ST elevation myocardial infarction (NSTEMI)/unstable angina (UA)

UA and NSTEMI are closely related conditions with similar clinical presentation, treatment, and pathogenesis but of varying severity. If there is biochemical evidence of myocardial damage, the condition is termed NSTEMI and, in the absence of damage, UA.


Unlike patients with a STEMI, where diagnosis is generally made on presentation in the emergency department, diagnosis of NSTEMI/UA may not be definitive on presentation and evolves over the subsequent hours to days. Therefore, management of patients with NSTEMI/UA is a progression through a number of risk-stratification processes dependent on history, clinical features, and investigative results, which in turn determine the choice and timing of a number of medical and/or invasive treatment strategies.

Fig. 5.16 is a summary of a recommended *integrated care pathway* illustrating a management plan for diagnosis and risk-directed treatment of a patient with STEMI/UA.

Clinical presentation

There are three distinct presentations:

- *rest angina* (angina when the patient is at rest)
- *new-onset severe angina*
- *increasing angina* (previously diagnosed angina which has become more frequent, longer in duration, or lower in threshold).


General examination (as indicated for all ACS (see  Acute coronary syndromes, p. 254)) must be undertaken, in particular to rule out pulmonary oedema, and assess haemodynamic stability, cardiac valve abnormalities, and diaphoresis.

Integrated management plan

We recommend that all patients follow a local integrated care pathway on presentation. The various stages are broadly outlined below. See relevant pages for further information.

Initial stabilization (see also  Acute coronary syndromes, p. 254):

- transfer the patient to an area with continuous ECG monitoring and defibrillator facility
- strict bed rest.
- give oxygen, aspirin 300 mg PO, SL nitrate, and mild sedation if required
- if pain persists give diamorphine 2.5–5 mg IV prn with metoclopramide 10 mg IV.

General investigations: similar to STEMI patients (see  STEMI: diagnosis, p. 258) including blood for FBC, biochemical profile, and markers of myocardial injury, lipid profile as well as CRP and thyroid function tests (TFTs) (if persistent tachycardia). Arrange portable CXR (rule out LVF, mediastinal abnormalities).

- Confirm diagnosis (see [📖 NSTEMI/UA: diagnosis, p. 292](#)).
- Risk stratification (see [📖 NSTEMI/UA: risk stratification, p. 294](#)) in order to determine appropriate medical and invasive treatment strategies. High-risk patients should be admitted to CCU and low/intermediate patients to monitored beds in step-down unit.
- Treatment is based on the patient's risk and includes:
 - medical:
 - anti-*ischaemic* (see [📖 NSTEMI/UA: medical management, p. 298](#))
 - antiplatelet (see [📖 NSTEMI/UA: medical management, p. 298](#))
 - antithrombotic (see [📖 NSTEMI/UA: medical management, p. 298](#))
 - *invasive strategies* (see [📖 NSTEMI: invasive vs. non-invasive strategies, p. 301](#))
- Secondary prevention and discharge

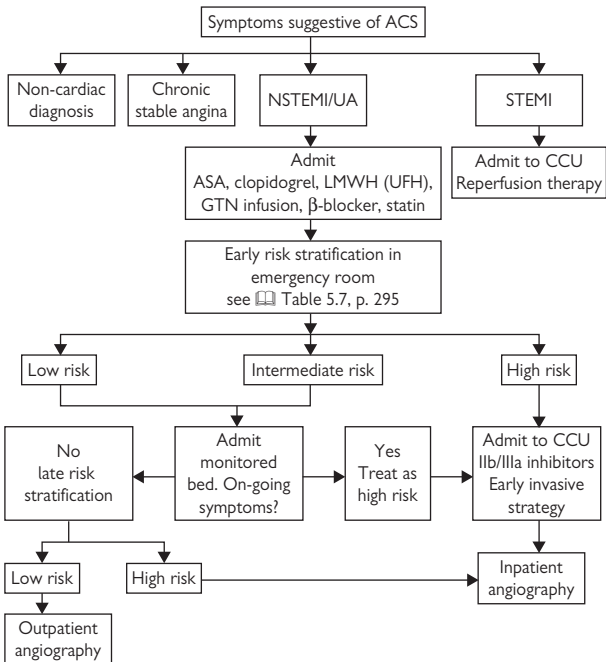


Fig. 5.16 NSTEMI/UA—integrated care pathway. Reproduced with permission from Ramrakha P, Moore K, and Sam A (2010). *Oxford Handbook of Acute Medicine*. 3rd edn. Oxford: Oxford University Press.

NSTEMI/UA: diagnosis

Diagnosis in NSTEMI/UA is an evolving process and may not be clear on presentation. A combination of history, serial changes in ECG, and biochemical markers of myocardial injury (usually over a 24–48 hour period) determine the diagnosis. Once a patient has been designated a diagnosis of ACS with probable/possible NSTEMI/UA (see [Non-ST elevation myocardial infarction \(NSTEMI\)/unstable angina \(UA\)](#), p. 290), they will require:


- *serial ECGs*—changes can be transient and/or fixed, especially if a diagnosis of NSTEMI is made. See [STEMI: diagnosis](#), p. 258 for localization of ischaemic areas.
 - ST-segment depression of ≥ 0.05 mV is highly specific for myocardial ischaemia (unless isolated in V_1 – V_3 , suggesting a posterior STEMI).
 - T-wave inversion is sensitive but non-specific for acute ischaemia unless very deep (≥ 0.3 mV).
 - rarely, Q waves may evolve or there may be transient/new LBBB.
- *serial biochemical markers of cardiac injury* are used to differentiate between NSTEMI and UA, as well as determine prognosis. We recommend levels at 6, 12, 24, and 48 hours after the last episode of pain. A positive biochemical marker (CK, CK-MB, or troponin) in the context of one or more of the aforementioned ECG changes is diagnostic of NSTEMI. If serial markers over a 24–72-hour period from the last episode of chest pain remain negative, UA is diagnosed:
 - *cardiac troponin T and I*—both are highly cardiac specific and sensitive, can detect ‘microinfarction’ in the presence of normal CK-MB, are not affected by skeletal muscle injury, and convey prognostic information (worse prognosis if positive). Troponins can be raised in non-atherosclerotic myocardial damage (cardiomyopathy, myocarditis, pericarditis) and should therefore be interpreted in the context of the clinical picture. Both TnT and TnI rise within 3 hours of infarction. TnT may persist upto 10–14 days and TnI up to 7–10 days. Results must be interpreted with caution in patients with chronic renal failure. See [Fig. 5.16 Non-ST elevation myocardial infarction \(NSTEMI\)/unstable angina \(UA\)](#), p. 290
 - *CK*—levels do not always reach the diagnostic twice upper limit of normal and generally have little value in diagnosis of NSTEMI
 - *CK-MB*—has low sensitivity and specificity; CK-MB isoforms improve sensitivity (CK-MB₂>1 U/L or CK-MB₂/CK-MB₁ ratio >1.5), but isoform assays are not widely available clinically
 - *myoglobin*—is non-cardiac specific, but levels can be detected as early as 2 hours after onset of symptoms. A negative test is useful in ruling out myocardial necrosis.
- *continuous ECG monitoring* can detect episodes of silent ischaemia and arrhythmia. Both have been shown to be more prolonged with NSTEMI than in UA.

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NSTEMI/UA: risk stratification

- NSTEMI/UA are a heterogeneous group of conditions with variable outcome. An assessment of risk for adverse outcome is vital to ensure formation of an adequate management plan.
- Risk stratification should begin on initial evaluation and continue throughout the hospital stay. At each stage, patients with a high chance of a poor outcome should be identified and managed appropriately.
- We recommend at least two formal risk-stratification processes.

Early risk stratification (Table 5.7)

This should take place on presentation and forms part of the initial assessment used to make a diagnosis. It involves a combination of clinical features, ECG changes, and biochemical markers of cardiac injury as demonstrated on  Non-ST elevation myocardial infarction (NSTEMI)/unstable angina (UA), p. 290. Patients are divided into high risk and intermediate/low risk.

- *High-risk* patients should be admitted to CCU, follow an early invasive strategy, and be managed with a combination of:
 - ASA, clopidogrel, LMWH (UFH), GP IIb/IIIa receptor inhibitors
 - anti-ischaemic therapy (first line β -blocker, GTN)
 - early invasive strategy (inpatient catheterization and PCI within 48 hours of admission).
- *Intermediate/low-risk* patients should be admitted to a monitored bed on a step-down unit and undergo a second inpatient risk stratification once their symptoms have settled, to determine the timing of invasive investigations. Initial management should include:
 - ASA, clopidogrel, LMWH (UFH).
 - anti-ischaemic therapy (first line β -blocker, GTN).
 - undergoing a late risk stratification in 48–72 hours from admission.

Late risk stratification (see NSTEMI/UA: late risk stratification, p. 296)

This involves a number of non-invasive tests to determine the optimal timing for invasive investigations in intermediate/low-risk patients. It is generally performed if there have been no further episodes of pain/ ischaemia at 24–48 hours after admission.

- Intermediate/low-risk patients who develop recurrent pain and/or ischaemic ECG changes at any point during their admission, heart failure, or haemodynamic instability in the absence of a non-cardiac cause should be managed as a high-risk patient (GP IIb/IIIa inhibitor and early invasive strategy).
- Table 5.7 is a summary of a recommended integrated care pathway combining diagnosis, risk stratification, and treatment.
- There are other risk-stratification assessment scores including Braunwald and TIMI. As recommended above, high-risk patients from these assessments should also follow an early invasive strategy, and intermediate/low-risk patients a more conservative strategy.

Table. 5.7 Short-term risk of death non-fatal MI in patients with UA

Feature	High risk (at least 1 of the following features must be present)	Intermediate risk (no high-risk feature but must have 1 of the following)	Low risk (no high- or intermediate-risk feature) but may have any of the following features)
History	Accelerating tempo of ischaemic symptoms in preceding 48 hours	Prior MI, peripheral or cerebrovascular disease or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 minutes) rest pain	Prolonged (>20 minutes) rest angina now resolved, with moderate or high likelihood of CAD Rest angina (<20 minutes) or relieved with rest or sublingual GTN	New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (>20 minutes) rest pain but with moderate or high likelihood of CAD
Clinical findings	Pulmonary oedema, most likely due to ischaemia New or worsening MR murmur S ₃ or new/worsening rales; hypotension, bradycardia, tachycardia Age>75 years	Age >70 years	
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	Elevated (e.g. TnT or Tnl >0.1 ng/mL)	Slightly elevated (e.g. TnT >0.01 but <0.1 ng/mL)	Normal

Adapted from American College of Cardiology Practice Guidelines.

NSTEMI/UA: late risk stratification

- The highest risk of adverse outcome in patients who are designated as intermediate/low risk on presentation is during the early phase of admission. Therefore, it is important that the second risk-stratification process occurs within 24–48 hours of admission if the patient is stable.
- Late risk stratification is based on one of the following non-invasive investigations.
- A patient is regarded as being at high risk of adverse outcome if they fulfil one of the features listed below. These patients should have inpatient cardiac catheterization.

Exercise ECG test

- Horizontal/down-sloping ST depression with:
 - onset at HR <120 bpm or <6.5 METS
 - magnitude of >2.0 mm
 - post-exercise duration of changes >6 min
 - depression in multiple leads reflecting multiple coronary distributions
- Abnormal systolic BP response:
 - sustained decrease of >10 mmHg or flat BP response with abnormal ECG
- Other:
 - exercise induced ST-segment elevation
 - VT
 - Prolonged elevation of HR

Stress radionuclide myocardial perfusion imaging

- Abnormal tracer distribution in more than one territory
- Cardiac enlargement

LV imaging

- Stress echocardiography:
 - rest EF <35%
 - wall motion score index of >1
- Stress radionuclide ventriculography:
 - rest EF <35%
 - fall in EF >10%

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NSTEMI/UA: medical management

Anti-ischaemic therapy

All patients should be treated with a combination of the below agents to ensure adequate symptom control and a favourable haemodynamic status (SBP 100–110 mmHg, pulse rate \approx 60). All patients should be treated with adequate analgesia, IV nitrates, β -blockers, and statins (if no contraindications). Other agents can also be added depending on the clinical picture.

- **Analgesia:** diamorphine 2.5–5 mg IV (with metoclopramide 10 mg IV). Acts as an anxiolytic and reduces pain and systolic blood pressure through venodilatation and reduction in sympathetic arteriolar constriction. Can result in hypotension (responsive to volume therapy) and respiratory depression (reversal with naloxone 400 mcg to 2 mg IV).
- **Nitrates:** GTN infusion (50 mg in 50 mL 1 M saline at 1–10 mL/h) titrated to pain and keeping SBP > 100 mmHg. Tolerance to continuous infusion develops within 24 hours, and the lowest efficacious dose should be used. Common side-effects are headache and hypotension, both of which are reversible on withdrawal of medication. *Absolute contraindication* is use of sildenafil (Viagra[®]) in the previous 24 hours. This can result in exaggerated and prolonged hypotension.
- **β -blockers:** should be started on presentation. Initially use a short-acting agent (e.g. metoprolol 12.5–100 mg PO tds), which, if tolerated, may be converted to a longer-acting agent (e.g. atenolol 25–100 mg od). Rapid β -blockade may be achieved using short-acting IV agents such as metoprolol. Aim for HR of \sim 50–60 bpm.
 - Mild LVF is not an absolute contraindication to β -blocker therapy. Pulmonary congestion may be secondary to ischaemic LV systolic dysfunction and/or reduced compliance. If there is overt heart failure, β -blockade is contraindicated and a calcium antagonist (amlodipine 5–10 mg od) can be used. By reducing heart rate and blood pressure, β -blockers reduce myocardial oxygen demand and thus angina. When either is used alone or in combination with nitrates and/or calcium antagonists, β -blockers are effective in reducing the frequency and duration of both symptomatic and silent ischaemic episodes.
- **Calcium antagonists:** diltiazem 60–360 mg PO, verapamil 40–120 mg PO tds). Aim to reduce HR and BP; these drugs are a useful adjunct to the three treatments above. Amlodipine/felodipine 5–10 mg PO od can be used with pulmonary oedema and in poor LV function. Calcium antagonists alone do not appear to reduce mortality or risk of MI in patients with UA. However, when combined with nitrates and/or β -blockers, they are effective in reducing symptomatic and silent ischaemic episodes, non-fatal MI, and need for revascularization.
- **Statins (HMG-CoA reductase inhibitors):** high-dose statins (atorvastatin 80 mg od) have been shown to reduce mortality and recurrent MI

in the acute setting. The role of statins in primary and secondary prevention of cardiovascular events is well documented.

- **ACE-Is:** unlike patients with STEMI, where early introduction of an ACE-I has significant prognostic benefits, specific trials in the NSTEMI/UA setting are lacking. However, there is good evidence that patients with both low and high risk of cardiovascular disease will benefit from long-term ACE inhibition (HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (European Trial on Reduction of cardiac Events with Perindopril in Stable Coronary Artery Disease) trials).

Antiplatelet therapy

All patients should be given aspirin and clopidogrel (unless there are contraindications)—GPIIb/IIIa antagonists to high-risk patients only.

- **Aspirin:** (75–300 mg PO) should be administered immediately in the emergency department and continued indefinitely (unless there are contraindications). It has been shown to consistently reduce mortality and recurrent ischaemic events in many trials. In patients with aspirin hypersensitivity or major GI intolerance, clopidogrel 75 mg od should be used.
- **Thienopyridines:** clopidogrel (75 mg od) should be given on admission to all patients with proven NSTEMI/UA, regardless of risk, and continued for at least 1 month and ideally for 9 months. Clopidogrel should be withheld for 5–7 days in patients requiring CABG, to reduce haemorrhagic complications. Clopidogrel is preferred over ticlopidine because of its rapid onset of action and better safety profile.
- **Glycoprotein IIb/IIIa antagonists:** there are multiple short- and long-acting commercially available molecules. These agents should be used in conjunction with aspirin, clopidogrel, and LMWH (or UFH). Eptifibatide and tirofiban should be used in high-risk patients with ongoing ischaemia and elevated troponin in whom an early invasive management strategy is not planned/available (<24 hours). In patients with an early invasive strategy, all GPIIb/IIIa antagonists can be used. Infusion is generally continued for 12 hours post-PCI. Taken as a group, these agents protect NSTEMI/UA patients from death and non-fatal MI during the acute phase of their presentation and 24 hours post intervention. See box on [p.300](#) for doses and administration regime.

Antithrombotic therapy

All patients should be given a LMWH (UFH).

- **Low molecular weight heparins (LMWH)** have been shown to be as good as, or superior to, UFH in short-term reduction of death, MI, and revascularization in patients with NSTEMI/UA. They should be used in conjunction with aspirin and clopidogrel in all patients on presentation and continued for 2–5 days after the last episode of pain and ischaemic ECG changes. Other advantages over UFH include subcutaneous administration, lack of monitoring, reduced resistance, and thrombocytopenia. The box on [p.300](#) lists the doses of various agents in use for NSTEMI/UA.

- *Unfractionated heparin* (UFH): multiple trials have demonstrated reduction of risk of death and MI in patients with UA/NSTEMI. UFH should be started on presentation as an alternative to LMWH in conjunction with aspirin and clopidogrel. Infusion should be continued for 2–5 days subsequent to the last episode of pain and/or ischaemic ECG changes. An initial bolus of 60–70 U/kg (maximum 5000 U) should be followed by an infusion of 12–15 U/kg/h (81000 U/h). The infusion rate should be altered to achieve an aPTT value of 1.5–2.0 times control. Coagulation should be checked initially every 6 hours, followed by once every 24 hours after two consistent values have been obtained.

Thrombolysis

There is no evidence to suggest that combining thrombolytic agents with aspirin, LMWH and conventional anti-ischaemic therapy is of benefit. In the TIMI IIIb trial, the rt-PA group had a worse outcome at 6 weeks, and the risk of bleeding was also greater with the thrombolysis group.

Doses of LMWH IIb/IIIa antagonists licensed for NSTEMI/UA

- LMWH
 - *Dalteparin*: 120 U/kg bd (max 10 000 U twice daily)
 - *Enoxaparin*: 1 mg/kg bd (100 U/kg twice daily)
- GPIIb/IIIa antagonists
 - *Abciximab* (ReoPro[®])—bolus 250 mcg/kg over 1 minute followed by IV infusion 125 ng/kg/min
 - *Tirofiban* (Aggrastat[®])—400 ng/kg/min for 30 minutes followed by IV infusion 100 ng/kg/min
 - *Eptifibatide* (Integrilin[®])—bolus 180 mcg/kg followed by IV infusion 2 mcg/kg/min

NSTEMI/UA: invasive versus non-invasive strategies

The current evidence supports early angiography and revascularization in patients who present with either high-risk features or intermediate/low-risk features with ongoing symptoms. Furthermore, low- and intermediate-risk patients who settle on medical therapy should undergo symptom-limited non-invasive stress testing to identify a cohort of patients with an increased risk of adverse outcome. This second group will also benefit from an early invasive management.

Patients managed with an early conservative strategy tend to have an increased need for anti-anginal therapy and rehospitalization for angina, and many undergo coronary angiography within a year.

The following groups are recommended to benefit from an early invasive strategy (inpatient cardiac catheterization and PCI):

- patients with high-risk features of NSTEMI/UA:
 - recurrent angina/ischaemic ECG changes despite optimal medical therapy
 - elevated troponin
 - new/presumed new ST-segment depression
 - chest pain with clinical features of heart failure (pulmonary oedema, new/worsening MR, S₃ gallop)
 - haemodynamic instability
 - sustained VT
- poor LV systolic function (EF <40%)
- patients allocated to low/medium risk in whom subsequent non-invasive testing demonstrates high-risk features
- PCI in the previous 6 months
- previous CABG
- patients with other co-morbidities (e.g. malignancy, liver failure, renal disease), in whom the risks of revascularization are not likely to outweigh the benefits.

NSTEMI/UA: discharge and secondary prevention

- The length of hospital stay will be determined by symptoms and the rate of progression through the NSTEMI/UA pathway. Generally, patients are hospitalized for 3–7 days.
- Secondary prevention remains of paramount importance and is similar in principle to STEMI patients.

Genetics of coronary artery disease: introduction

A number of studies (e.g. Framingham) have established family history as an independent risk factor for coronary artery disease (CAD). Approximately 50% of susceptibility to CAD is believed to be genetic; a Swedish twin study showed 57% and 38% heritability of fatal coronary events in males and females respectively.¹ In addition, premature CAD is known to show greater heritability than that occurring later in life. The majority of cases of CAD result from complex interactions between genetic and environmental risk factors, with only a relatively small proportion secondary to well-defined monogenic disorders.

1 Zdravkovik S, Wienke A, Pedersen NL, Marenberg ME, Yashin AI, De Faire U. (2002). Heritability of death from coronary heart disease: a 36 year follow-up of 20,966 Swedish twins. *J Intern Med* **252**: 247–54.

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Monogenic causes of coronary artery disease

These are rare diseases characterized by Mendelian inheritance (see Table 5.8 for examples). The most commonly identified monogenic cause for CAD is familial hypercholesterolaemia (FH), an autosomal co-dominant condition that is present in 5–10% of patients who develop CAD before the age of 55 years. FH is caused by mutations affecting the LDL receptor, apolipoprotein B, and PCSK9 (proprotein convertase subtilisin/kexin type 9); these mutations cause elevated plasma LDL-C and accelerated atherosclerosis, with subsequent premature CAD. Homozygotes (frequency 1:1 000 000) have no functional LDL receptors and suffer very premature CAD; the majority will die before the age of 30 years, in the absence of treatment. The population prevalence of heterozygous FH is estimated at 1:500, but may be much higher in some populations (e.g. Afrikaners and French Canadians), secondary to ‘founder’ effects. Many of those affected by FH remain undiagnosed.

Guidelines for the diagnosis and management of FH were published by the National Institute for Health and Clinical Excellence (NICE) in 2008.¹ A clinical diagnosis of FH should be suspected in adults who have markedly elevated total cholesterol (> 7.5 mmol/L), particularly if there is a positive family or personal history of premature CAD. Clinical diagnosis of definite or possible FH should be based on the Simon Broome criteria, as outlined opposite; patients diagnosed with FH should be referred to a specialist lipid clinic for DNA testing and cascade testing of relatives. Those diagnosed with homozygous FH, or with symptoms and/or signs of CAD should be referred urgently to a cardiologist. First-line treatment is with statins, aiming for a $\geq 50\%$ reduction in LDL-C, although dual treatment with a statin and ezetimibe may be required to meet this target. Fibrates, bile acid sequestrants, and nicotinic acid may be initiated by a specialist in FH if initial treatment is contraindicated, is not tolerated, or is ineffective.

¹ NICE (2008). *Clinical Guidelines and Evidence Review for Familial Hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia*. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

Table 5.8 Examples of monogenic disorders causing coronary artery disease

Condition	Genes	Clinical effects
Familial hypercholesterolaemia	<i>LDLR, PCSK9, APO-B</i>	Raised plasma total and LDL cholesterol, tendon xanthomata
Sitosterolaemia	<i>ABCG5, ABCG8</i>	Raised plasma phytosterols, tendon xanthomata, haemolysis
Tangier disease	<i>ABCA1</i>	Reduced plasma HDL cholesterol, enlarged yellow tonsils, hepatosplenomegaly
Homocystinuria	<i>CBS</i>	Raised urinary homocysteine, delayed development, Marfan-like physique, thromboembolic events

LDLR = low density lipoprotein receptor, PCSK9 = proprotein convertase subtilisin/kexin type 9, APO-B = apolipoprotein B, ABCG5/8 = ATP binding cassette proteins, type G, ABCA1 = ATP binding cassette transporter 1, CBS = cystathionine beta-synthase

Simon Broome criteria for diagnosis of FH in adults (after exclusion of secondary causes of hyperlipidaemia)

Definite FH

- Total cholesterol >7.5 mmol/L (LDL > 4.9 mmol/L), pretreatment (or highest on treatment), and presence of tendon xanthomas in the patient or 1st- or 2nd-degree relative

or

- evidence of a mutation in the LDL receptor, apolipoprotein B, or PCSK9

Possible FH

- Total cholesterol >7.5 mmol/L (LDL >4.9 mmol/L) pretreatment (or highest on treatment).

and one of the following:

- family history of MI (< 50 years in 2nd-degree relative or <60 years in 1st-degree relative)
- family history of raised cholesterol (>7.5 mmol/L in adult 1st- or 2nd-degree relative; >6.7 mmol/L in child or sibling aged <16 years)

Genes conferring increased risk of coronary artery disease (polygenic CAD)

Evidence suggests that CAD in most patients results from a combination of genetic predisposition and environmental risk factors. In particular, premature CAD is thought to arise in individuals with a genetic predisposition who are then exposed to a high-risk environment. However, with the exception of the monogenic disorders described above, attempts to identify the genes responsible for conferring an increased risk of CAD have met with only limited success. Atherosclerosis is a complex process, involving interactions between a number of physiological pathways, including lipoprotein metabolism, inflammation, maintenance of endothelial integrity, and coagulation. Genetic polymorphisms affecting any of these pathways may therefore contribute towards an increased risk of CAD. In addition, well-established risk factors for CAD such as hypertension, diabetes, and obesity are also polygenic traits and will interact with other susceptibility genes and environmental risk factors (e.g. smoking) in the development of atherosclerosis.

Historically, 'candidate gene' studies have been used in an attempt to identify risk factor genes for CAD; candidate genes are selected based on their role within one of the physiological pathways responsible for atherosclerosis. One of the genes most successfully identified from such studies is apolipoprotein E, of which there are 3 alleles: *APOE2*, *APOE3*, and *APOE4*. *APOE3* is the most common allele in European populations; the *APOE2* and *APOE4* alleles are associated with reduced and elevated plasma LDL-C respectively. A meta-analysis of 121 studies in which coronary outcomes were evaluated showed an odds ratio for CAD of 0.80 in carriers of the *APOE2* allele, and 1.06 in carriers of the *APOE4* allele, compared to individuals who were homozygous for *APOE3*.¹ Individuals carrying the *APOE4* allele and who also smoke may show a particularly elevated risk for CAD,² although this remains controversial.

Additional genes that have been implicated include those for lipoprotein lipase, thrombospondin, prothrombin, endothelial nitric oxide synthase (eNOS), myocyte enhancer factor 2A (MEF2A), and 5-lipoxygenase activation protein (FLAP). However, inconsistent results have been obtained for a number of these genes. More recently, following sequencing of the human genome, a number of independent genome-wide association studies have identified a single locus on chromosome 9p21 as being associated with an increased risk of CAD³. A cluster of genes involved in control of the cell cycle have been identified in this region; since cellular proliferation is an essential step in the development of the atherosclerotic plaque, this may provide a mechanism for the role of this locus in the development of CAD.

1 Bennet AM, Di Angelantonio E, Ye Z, et al. (2007). Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA* **298**: 1300–11.

2 Humphries SE, Talmud PJ, Hawe E, Bolla M, Day IN, Miller GJ (2001). Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospective study. *Lancet*. **358**: 115–19.

3 McPherson R, Pertsemidis A, Kavaslar N, et al. (2007). A common allele on chromosome 9 associated with coronary heart disease. *Science* **316**: 1488–91.

Genetic testing for coronary artery disease

In patients where a monogenic cause of CAD is diagnosed on clinical assessment, it is desirable to perform genetic testing to identify the mutation(s) responsible and allow relatives to be screened. A number of methods are now available for identifying the mutations responsible for causing FH, and the current NICE guidelines recommend that genetic testing is offered to all patients with a clinical diagnosis of FH; current methods can detect the FH-causing mutation in 70–80% of patients with a definite diagnosis of FH based on the Simon Broome criteria. Unfortunately, the available techniques are not 100% sensitive; therefore the absence of an identified mutation does not exclude a diagnosis of FH. Once a mutation is identified, NICE guidelines recommend cascade testing for the mutation in 1st-, 2nd-, and, if possible, 3rd-degree relatives. Appropriate primary prevention with cholesterol-lowering drugs can then be instituted to reduce the risk of CAD; this results in a 48% reduction in coronary heart disease mortality.¹

Unfortunately, genetic testing is not yet available for the majority of patients, in whom CAD results from the interactions between polygenic susceptibility and a high-risk environment. However, evidence suggests that those patients who carry ≥ 7 'risk' alleles (from a group of 10 identified candidate genes) have an increased odds ratio (4.51) for CAD when compared to those carrying 3–4 'risk' alleles.² Any future genetic test for such patients will need to incorporate a number of polymorphisms in a range of genes, and be assessed in the context of environmental risk factors, if it is to be used for clinical risk stratification.

¹ Neil A, Cooper J, Betteridge J, et al. (2008). Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* **29**: 2625–33.

² Drenos F, Whittaker JC, Humphries SE (2007). The use of meta analysis risk estimates for candidate genes in combination to predict coronary heart disease risk. *Ann Hum Genet* **71**: 611–19.

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Cardiac catheterization and intervention

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Radiation protection in the catheterization laboratory

All practitioners delivering ionizing radiation during medical procedures must attend a radiation protection course (IRMER, Ionising Radiation Medical Exposure Regulations 2000). Furthermore, staff working in the catheterization laboratory should be issued with radiation-monitoring badges, for the body and neck, which should always be worn while in the lab. These badges should be checked monthly to assess doses of radiation received by individual members of staff. No unnecessary staff should be within the catheterization lab during a procedure, and all staff that need to be in the lab should be as far from the tube as practical.

Minimizing patient dose

- Minimize screening time and minimize acquisition time.
- Keep the distance between the X-ray tube and image intensifier to a minimum.
- Use collimation and cones to minimize the irradiated area.
- Use lower magnifications when possible.
- Use the lowest number of frames/second to allow adequate imaging.
- For prolonged procedures, the intensifier should be moved regularly, a few degrees, to try to minimize the possibility of skin burns.

Minimizing operator dose

- Lead aprons and lead collars should be worn.
- Additional screening should be used where available:
 - lead apron below table.
 - mobile lead screen to go between the operator and source.
- As above, minimize X-ray exposure by reducing screening and acquisition time.
- Some projections (e.g. left anterior oblique (LAO)) give much higher scatter of X-ray, and operators should be aware of this.


The dose for an interventional cardiologist has been calculated as 60 mSv (based upon 150 working days per year and 4 interventions per day). The calculated effective dose if the operator wears the correct lead apron and thyroid collar is less than 5 mSv/year. The maximum allowed dose is 20 mSv/year.

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Vascular access: the femoral artery

Procedure for femoral artery access

- The standard approach for left heart catheterization is the right common femoral artery.
- The artery is located by palpating below the inguinal ligament, the ideal position for puncture being approximately 3 cm below the inguinal ligament and slightly lateral to the position of the vessel.
- The area should be anaesthetized generously with local anaesthetic (usually 10 mL of 2% or 20 mL of 1% lidocaine). Warn the patient of 'pins and needles' or transient numbness in the leg that may be caused by the effects of lidocaine on the femoral nerve.
- A small incision (3–5 mm) is made in the overlying skin. The tissue underlying this incision may then be dilated; commonly this is done by using curved 'mosquito' forceps.
- The procedure used to puncture the artery is known as the 'Seldinger technique'. A hollow needle is introduced slowly; it is often possible to feel the pulsations of the artery via the needle before the vessel is punctured. When the needle is introduced into the vessel, pulsatile flow confirms its position in the arterial lumen. At this point a 0.035" wire can be advanced into the vessel and towards the heart; this should be performed under fluoroscopic guidance.
- The needle is then withdrawn and a haemostatic sheath (usually 5–8 Fr diameter) is introduced over the wire; the haemostatic sheath allows the introduction of a guide wire and catheter into the femoral artery, while preventing excess bleeding from the femoral puncture site.

Sheath removal (see  Vascular access site management, p. 316)

- This can be performed immediately after diagnostic angiography, or after an interval of 4–6 hours if heparin has been administered.
- Haemostasis can be achieved by manual compression or by using a compression device (e.g. Femstop™).
- Vascular closure devices (e.g. Angioseal™ or Perclose™) allow earlier removal of sheaths in anticoagulated patients and may reduce bleeding complications.

Complications

- Femoral artery dissection
- Femoral artery pseudoaneurysm
- Distal embolization
- Haematoma
- Retroperitoneal haemorrhage/haematoma (particularly with high punctures of the femoral artery above the inguinal ligament).

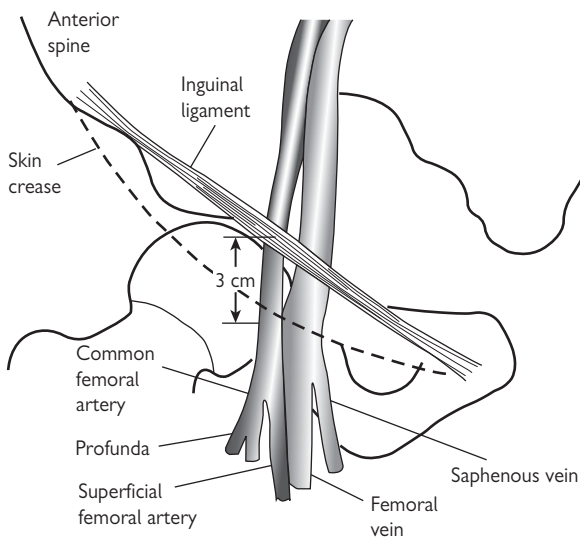


Fig. 6.1 Anatomy of the inguinal canal: the femoral vein lies medial to the femoral artery. The arterial puncture should be made 73 cm below the inguinal ligament.

Vascular access: the radial artery

The radial approach for coronary angiography is now widely accepted. There are several advantages, including a reduction in vascular complications, and the ability to mobilize patients immediately following their procedure. Patient selection for radial access should include palpation of the radial artery to confirm pulsations are present and then an Allen's test. In the absence of robust supply via the ulnar artery, the radial approach should not be used.

Procedure for radial artery approach

- Consent patient.
- Perform Allen's test.
- Remove all jewellery from arm, shave area, and disinfect.
- Local anaesthesia: Use 1–2 mL 2% lidocaine instilled via a 25 gauge needle (i.e. enough to anaesthetize, but not to distort the anatomy).
- The artery should be palpated with the index and middle fingers, the index finger lifted, and the artery punctured at 45 degrees. The artery should be punctured as proximally as possible, and care should be taken to avoid the flexor retinaculum.
- Once pulsatile flow is obtained, a guide wire can then be advanced through the needle and into the vessel.
- It is usual to make a small incision in the skin to allow passage of an arterial sheath. Care should be taken not to damage the radial artery while making this incision. Thus the blade should be used to incise in the longitudinal plane, rather than transversely, to reduce the risk of completely transecting the artery.
- A variety of long and short sheaths are commercially available. The advantage of long sheaths is that they minimize trauma to the radial artery.

Complications

Radial artery spasm is the commonest complication of radial artery puncture and sheath introduction. There are various techniques to try and prevent radial artery spasm from occurring, these include:

- careful patient selection, avoiding small and difficult-to-palpate radial arteries
- adequate patient sedation if required—pain provokes spasm
- the use of a 'cocktail' of drugs introduced directly into the radial artery. A variety of different regimens have been described. We use 1 mg isosorbide dinitrate, 2.5 mg verapamil, and 2500 U heparin made up to 10 mL with normal saline. Repeated doses of nitrates or verapamil (up to 5 mg) given directly into the sheath or in the catheter may be required
- shorter sheaths may be better tolerated
- some sheaths have a hydrophilic coating to try to reduce spasm, and for less discomfort on removal
- always use a guide wire to straighten catheters prior to removal from the aortic arch through the radial sheath.

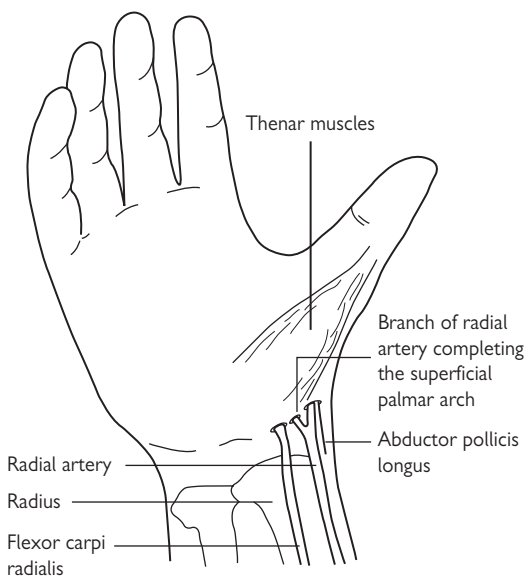


Fig. 6.2 Radial artery anatomy.

Common radial pitfalls and solutions

- Radial loop:
 - 360 degree loop in radial artery. This may be negotiated with a hydrophilic guide wire or angioplasty wire before straightening with a catheter.
- Tortuosity in proximal vessels:
 - this also may be negotiated as above; manoeuvres such as breath holds and gentle ipsilateral arm traction may help.
- Recurrent radial artery:
 - anatomical variant arising from the radial artery below the elbow; may be blind ending. Contrast injection may provide a useful roadmap.
- Difficulty accessing the ascending aorta:
 - breathholding may help to straighten the access route.

Vascular access site management

Femoral sheath removal

Femoral sheaths should only be removed by fully trained members of staff. After diagnostic coronary angiography, when no or little heparin is given, the sheath may be removed immediately. Direct pressure should be applied just proximal to the site of the skin puncture for 5 to 10 minutes. After angioplasty, it is routine to wait for between 4 to 6 hours, an activated clotting time (ACT) < 150 s suggests that the effect of systemic heparinization is wearing off, and it is acceptable for the sheath to be removed. Femoral clamps (FemoStop[®], RADl Medical Systems) can be used to reduce bleeding complications in patients.

Radial sheath removal

Radial sheaths are removed immediately after both diagnostic angiograms and angioplasty, as the position of the artery renders compression more simple. Compression bands (RadiStop[®], RadiMedical Systems USA, TR-Band[™], Terumo). See Fig. 6.3.

Vascular closure devices

Until recently, mechanical compression was the only method for controlling bleeding from vascular access sites in the groin. Larger sheaths and the advent of the more widespread use of glycoprotein (GP) IIb/IIIa inhibitors have increased the risk of bleeding, and made homeostasis more difficult. Recently, various closure devices have been introduced; the aim of these is to increase patient comfort, and reduce puncture-related complications.

Suture-based closure devices

Perclose[®] (Abbot Vascular, USA): this delivers a suture to the arterial puncture site. The device is sheath-like in nature; needles are positioned above the sheath in the handle, and are deployed by a plunger. A 'clincher' that performs a knot-tying function completes a sliding knot.

Collagen-based closure devices

Devices that utilize a bioresorbable collagen plug that is deposited at the site of arteriotomy via a sheath; such devices include the VasoSeal[®] (Datascope Corp, USA) and Angio-Seal[®] (St Jude Medical, USA, see Fig. 6.4).

Other mechanical closure devices

StarClose[®] features a Nitinol[®] clip that is designed to promote the primary healing process to achieve a secure closure of femoral artery access sites following diagnostic or interventional vascular procedures. This clip provides 360-degree tissue apposition for rapid healing and haemostasis.

Drug-based closure devices

Clo-Sur[®] PAD (Medtronic, USA): this device contains a naturally occurring biopolymer polypropylate acetate. This polymer has a coagulant property when brought into contact with heparinized blood. The device is placed over the puncture and the haemostatic sheath is removed. Direct continuous pressure is applied until haemostasis is achieved.



Fig. 6.3 TR Band™ Radial access closure device. Reproduced with permission from www.terumo.com.

Radial closure device: TR Band™ (see Fig. 6.4)

How to place a TR band

- Position the spot on the TR Band™ over the radial puncture site, with the sheath *in situ*.
- An assistant should inflate the syringe with the minimal amount of air (usually 12–15 mL) needed to achieve haemostasis, while ensuring the radial artery remains palpable. The operator simultaneously withdraws the sheath from the radial artery.
- Add/remove additional air if needed.
- Perform regular neurovascular hand observations.
- Slowly deflate the TR Band™ over a few hours until bleeding has stopped.

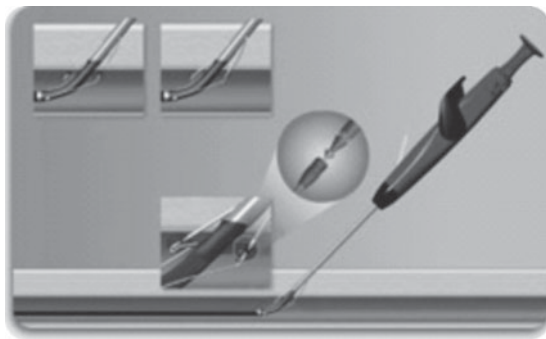


Fig. 6.4 Angioseal™ vascular closure devices.

Coronary angiography

Pre-shaped coronary angiographic catheters

The catheters used in diagnostic coronary angiography come in a wide variety of preformed shapes. In the UK, the most commonly used pre-shaped catheters are the Judkins Left 4 and Judkins Right 4 (known as the JL4 and JR4 respectively), used to image the left and right coronary arteries, and the pigtail catheter, used for left ventriculography. The diameter of catheters is measured in French gauge (Fr); catheters between 4Fr (0.053") and 8 Fr (0.105") are commonly used.

Commonly used cardiac catheter shapes

See Fig. 6.5.

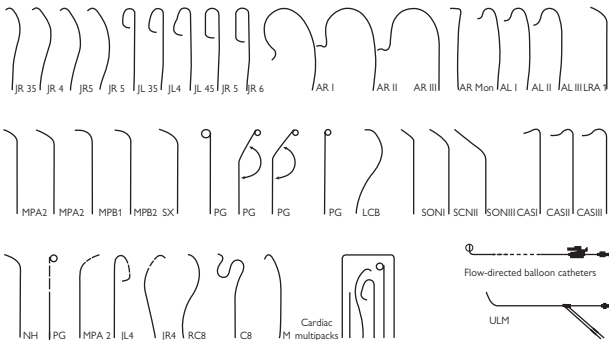


Fig. 6.5 Commonly used cardiac catheter shapes.

Catheter advancement and manifold usage

A 'J'-tipped 0.035" guide wire is placed within the flushed catheter, which is then passed into the haemostatic sheath. The guide wire is advanced ahead of the catheter under fluoroscopic guidance, until it reaches the aortic root, just above the aortic valve. The catheter is then advanced to this position and the guide wire is removed. To ensure that no air or clot is within the catheter, a small volume of blood (5 mL) is aspirated from the catheter directly into a syringe and discarded. The catheter is then carefully connected to a two-way manifold, which allows pressure monitoring, saline flushing, and contrast injection through a closed system.

Contrast injection

Great care must be taken at all times to ensure that air is not injected into the coronary arterial tree. The injection syringe should be filled with contrast from the reservoir, and then the syringe held with the plunger elevated so that any air bubbles rise to the top of the syringe. Contrast should then be injected at a continuous rate, aiming to fully opacify the coronary vessel of interest. Care should be taken that the pressure trace is normal before injection—damping suggests an ostial stenosis, excessively deep intubation, or selective intubation of a branch.

Coronary angiography/left ventriculography

Left coronary artery

- The 50° left anterior oblique (LAO 50) is the best projection for cannulation of both the left and right coronary ostia.
- In reality however, the left coronary ostium is often cannulated with the tower in the anteroposterior (AP) position.
- The JL4 catheter will almost invariably cannulate the left coronary ostium without manipulation.
- In patients with large aortic roots (large, hypertensive patients), the JL5 (with a larger curve) may be needed, and, conversely, a smaller root may need a smaller catheter curve, the JL3.5.

Right coronary artery

- The LAO 50 projection is best used for cannulation of the right coronary ostium.
- The JR4 catheter is introduced to the aortic root, until it lies 1–2 cm above the aortic valve.
- The catheter is then rotated ('torqued') in a clockwise direction, such that the catheter tip rotates towards the right coronary ostium. It may be necessary to reduce the torque to prevent the catheter from over-shooting.
- There is often a noticeable lateral movement as the catheter enters the artery.
- Before contrast is injected, it must be ensured that the pressure tracing transduced from the tip of the catheter is not damped.
- NB: damping can suggest that the catheter has selectively intubated the conus branch of the right coronary artery, and injection of contrast into this vessel can induce ventricular arrhythmias.

Left ventriculography

- Position a pigtail catheter a few centimetres above the aortic valve and pull the wire back 5–10 cm to make the catheter tip soft, and push gently (the catheter may cross at this point).
- If the catheter does not cross, apply torque as it is gently withdrawn.
- If this technique is not successful, use a straight soft-tipped guide wire and catheters that allow that guide wire to be 'pointed' at the valve (e.g. AL1 or JR4). This may improve the chances of crossing the valve.
- Once the catheter has been placed in a stable (free of ectopics) position in the mid-LV cavity, connect to the manifold and measure the pressure.
- Disconnect the manifold catheter connected to a power injector and expel all air.
- Set the injection rate: typically 25–30 mL of contrast at a rate of 10 mL/s. Warn the patient about hot flush and the feeling of extra systoles.
- When the left ventriculogram has been performed, the catheter is reconnected to the manifold to allow pressure recording as the catheter is withdrawn across the aortic valve (the pullback pressure).

Interpreting the coronary angiogram

Left coronary artery (LCA) angiographic views (Fig. 6.6)

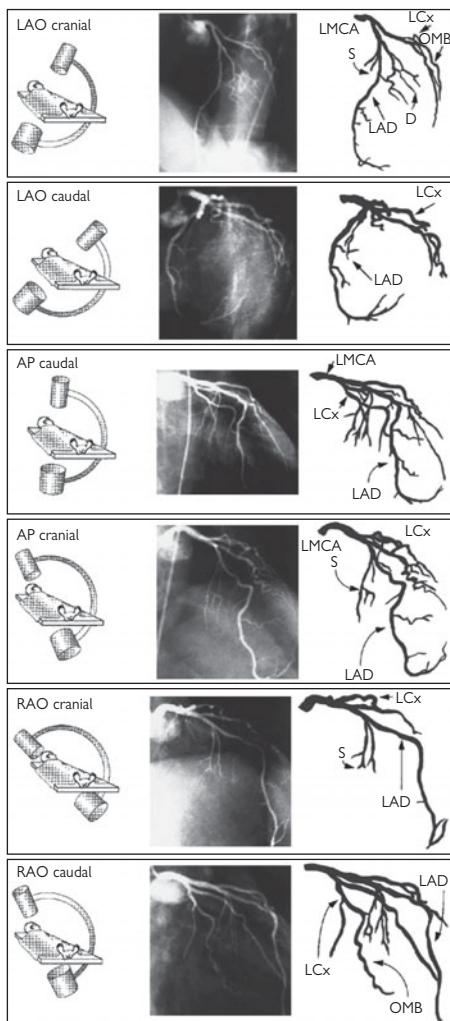


Fig. 6.6 LCA angiographic views. Reproduced with permission from Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*. 5th ed. Philadelphia: WB Saunders.

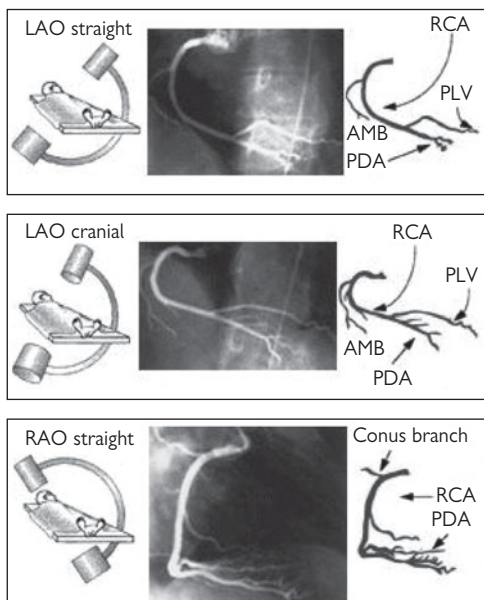
Right coronary artery (RCA) angiographic views (Fig. 6.7)

Fig. 6.7 RCA angiographic views. Reproduced with permission from Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*. 5th ed. Philadelphia: WB Saunders.

Angiographic study of grafts

It is important to study the surgical record to ascertain how many grafts were placed at the time of the operation. Sometimes, useful information (often from a surgeon's diagram) can be obtained as to the position in the ascending aorta that the grafts arise from. As a rule, leftwards-facing grafts are best cannulated from the RAO 50 projection, and rightwards-pointing grafts are best cannulated in the LAO 50 projection. It may be necessary to perform an aortogram to visualize the position of grafts. Specialist catheters (e.g. the left coronary bypass catheter or LCB) have been designed to aid cannulation of grafts.

There is usually a predictable anatomy:

- patent ductus arteriosus (PDA) grafts originate from the right anterior aspect of the aorta and run vertically to the inferior surface of the heart
- obtuse marginal (OM) grafts originate from the left anterior aspect of the aorta and arc towards the posterolateral surface of the heart
- left anterior descending (LAD) and diagonal grafts originate from an intermediate position and run laterally towards the anterior interventricular groove.
- arterial grafts improve patency rates in coronary artery bypass graft (CABG) and are preferred in contemporary surgery. Left internal mammary artery (LIMA) grafts are usually accessed via the femoral route, but may also be accessed via the left radial approach. Right internal mammary artery (RIMA) grafts are less often used, and can be approached via either the femoral or right radial route.
- the left subclavian artery is accessed using a standard JR or multipurpose catheter. Care must be taken when advancing catheters up the subclavian artery. A JR catheter may engage the LIMA directly or may need to be exchanged over a long wire for an internal mammary artery catheter.
- small contrast injections may be needed to identify the LIMA ostium.
- coronary injections should be acquired in different orthogonal planes to adequately visualize the LIMA and its subtended territory, particularly the point of insertion.
- the patient should be warned that they will feel a warm flushing feeling in their arm and neck.
- the catheter should be disengaged under fluoroscopic screening and carefully removed over a wire.

Common aortic positions for placement of saphenous vein graft (SVG) (Fig. 6.8)

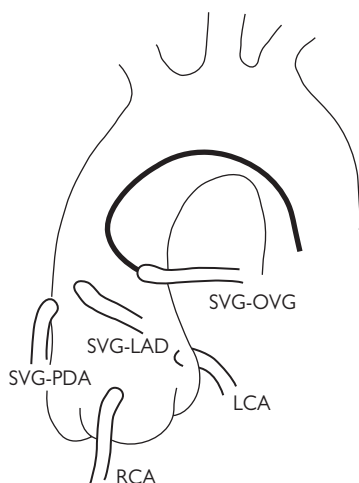


Fig. 6.8 Common aortic positions for placement of SVG. OVG = omniflow vascular graft. Reproduced with permission from Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*. 5th ed. Philadelphia: WB Saunders.

Complications of angiography

Peripheral vascular complications

Haematoma

The incidence of haematoma formation is related to the following factors:

- length of time the sheath is left in place
- gauge (size) of the sheath
- anticoagulation
- risk factors, e.g. hypertension, obesity, and pre-existing peripheral vascular disease
- technique of sheath removal.

Features that suggest a haematoma may require further investigation are an overlying bruit, expansile mass, and a large tense swelling.

Pseudoaneurysm (Fig. 6.9)

A pseudoaneurysm represents a rupture of the femoral arterial wall at the site of puncture, with the formation of a false aneurysm involving the media and adventitia. It is best visualized on ultrasound examination. Small pseudoaneurysms can often be managed by direct compression; however, large pseudoaneurysms may require thrombin injection, or surgical intervention.

Haemorrhage

If prolonged, then direct pressure (either manually or using a clamping device) may be needed. Heparin anticoagulation can be reversed using protamine.

Limb ischaemia

This is rare, and usually occurs in patients with pre-existing limb ischaemia. If limb ischaemia is suspected, then urgent review by the vascular surgical team should be sought.

Contrast reactions

Mild contrast reactions such as rash, urticaria, blurred vision, and rigors are relatively common. These symptoms may settle spontaneously, but are often treated with a combination of IV chlorphenamine 10 mg and IV hydrocortisone 100–200 mg. Anaphylactic reactions are rare; these should be treated with chlorphenamine and hydrocortisone, but also plasma expanders and IM adrenaline.

Vasovagal reactions

These are common both during angiography and at the time of sheath removal, and characterized by hypotension and bradycardia. They are treated with IV atropine and volume expanders.

Arrhythmia

Brief episodes of supraventricular tachycardia (SVT) are common and often transient. During catheter manipulation (especially in the left ventricle (LV)), salvos of VT are common. Ventricular fibrillation (VF) may occur during coronary artery injection, and should be treated with rapid defibrillation.

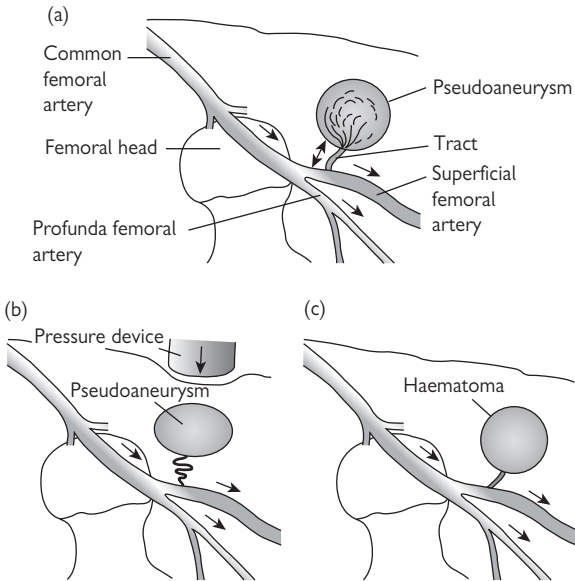


Fig. 6.9 Anatomy of a pseudoaneurysm. (a) Bleeding along a small tract allows blood to collect within the extravascular tissues. Manual compression fails to obliterate the tract (b), and allows the haematoma to persist. Failure of thrombosis of the haematoma produces an extravascular collection with persistent connection and flow from the main artery (c). This can be visualized on ultrasound scan (USS).

Radial arterial complications

One of the main advantages of the radial route is a reduction in complication rates.

Bleeding

This is more easily managed with direct pressure than from the femoral route.

Compartment syndrome

This is a rare, but potentially catastrophic complication.

Pseudoaneurysm

Rare. Manage as per femoral pseudoaneurysm.

Radial artery occlusion


The rate of radial artery occlusion following radial artery cannulation is unclear—but is probably between 1% and 5%. The rate of occlusion is reduced with smaller sheath sizes, hydrophilic sheaths, and heparin administration.

Right-heart catheterization

Indications for right-heart catheterization include:

- evaluation of cardiac shunts
- evaluation of valvular heart disease
- dyspnoea not explained by non-invasive investigation
- investigation for pulmonary hypertension
- work-up for cardiac transplantation
 - investigation for pulmonary hypertension and transplantation should only be performed in specialist centres.

The acute settings in which right heart catheterization can be helpful (e.g. intensive drug therapy in cardiogenic shock) will not be discussed here.

Access to the right heart is usually achieved via the right femoral vein (RFV). The RFV is located 0.5 cm to 1 cm medial to the femoral arterial pulsation (see  Vascular access: the femoral artery, Fig. 6.1, p. 313). An 18-gauge needle, attached to a syringe that is partially filled with saline, can be used to locate the position of the vein, followed by the larger-bore needle. When venous blood is freely aspirated, a 0.035" guide wire is passed into the vein, using a technique similar to femoral artery cannulation, and a haemostatic sheath introduced.

Right-heart catheterization protocol

- A 'multipurpose' catheter or balloon-tipped catheter may be used.
- Ensure that the catheter is flushed, and that the transducer is correctly zeroed.
- Advance the catheter to the inferior vena cava (IVC), and further to the right atrium. Record the phasic and mean pressures.
- It is customary to then advance the catheter to the pulmonary artery wedge position. Advance into the RV. A combination of rotation of the catheter and gentle traction will allow the catheter to flick upwards into the right ventricular outflow tract (RVOT). It can then be advanced into the main pulmonary artery (PA) and out to the periphery. Occasionally, the guide wire is necessary to achieve this.
- Advance the catheter to the pulmonary capillary wedge position, and record phasic and mean pressures.
- With a pigtail catheter in the LV, measure and record the LV pressures. Record simultaneous pulmonary capillary wedge pressure (PCWP) and LV pressure, ensuring that the scale allows interpretation of the end-diastolic pressures with accuracy (to assess for mitral valve (MV) gradient).
- Withdraw the wedge catheter slightly and record pulmonary artery phasic and mean pressure. Obtain oxygen saturations from the main PA (also right and left pulmonary arteries (RPA and LPA) if a PDA is suspected).
- Withdraw the pulmonary catheter to the right ventricle (RV). Measure and record simultaneous RV and LV pressures.
- Withdraw the catheter to the RA and measure the pressures again.

- The LV catheter should be pulled back to the ascending aorta while the pressure is being monitored to record any pull-back gradient. Aortic saturations should be measured to allow calculation of cardiac output (see Fig. 6.10) and to compare with saturations from the right side if a shunt is suspected.
- For shunts, a full saturation run should be performed (superior vena cava (SVC); high, mid, and low right atrium (RA), IVC, RV; main, right, and left pulmonary artery (MPA, RPA, LPA); etc.).

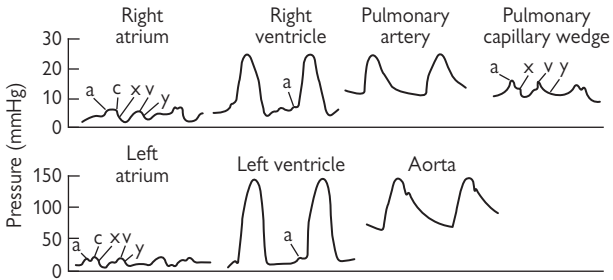


Fig. 6.10 Cardiac catheterization—normal pressure waveforms.

Cardiac output and left ventricular function

Cardiac output is most often measured using the thermodilution method with a pulmonary flotation catheter.

Cardiac output can also be measured using the Fick principle, which assesses the difference between the pulmonary arterial and aortic O₂ saturation.

$$\text{Cardiac output (L/min)} = \frac{\text{oxygen consumption (mL/min)}}{(\text{Ao SaO}_2 - \text{PA SaO}_2) \times \text{Hb} \times 1.34}$$

Where Ao = aorta; Hb = haemoglobin; PA = pulmonary artery; SaO₂ = arterial oxygen saturation.

Systemic and pulmonary vascular resistance

Pulmonary vascular resistance (PVR) is an important prognostic factor in patients with valvular heart disease, heart failure, and cor pulmonale. The measurement of PVR and systemic vascular resistance (SVR) is especially important in patients being assessed for cardiac transplantation.

PVR and SVR are measured in Woods units (mmHg/L/min) or dynes/cm⁵, with 80 dynes/cm⁵ = 1 Woods unit.

$$\text{Cardiac output} = \frac{\text{mean aortic pressure} - \text{mean right atrial pressure}}{\text{systemic vascular resistance}}$$

$$\text{Cardiac output} = \frac{\text{mean PA pressure} - \text{mean left atrial pressure}}{\text{pulmonary vascular resistance}}$$

Cardiac catheterization in valve disease

Valve stenosis

Several parameters can be assessed during cardiac catheterization.

- **Peak-to-peak gradient:** aortic and LV pressures are recorded during withdrawal of the pigtail catheter across the aortic valve. The gradient is the difference between peak aortic and peak LV pressure.
- **Peak instantaneous gradient:** more accurate and measured using a double-lumen pigtail catheter.
- **Mean gradient:** the mean pressure gradient measured using planimetry of the area by aortic and LV pressure traces. This can be used to calculate the valve area using the Gorlin equation, and a similar method can be used to assess the mitral valve area.

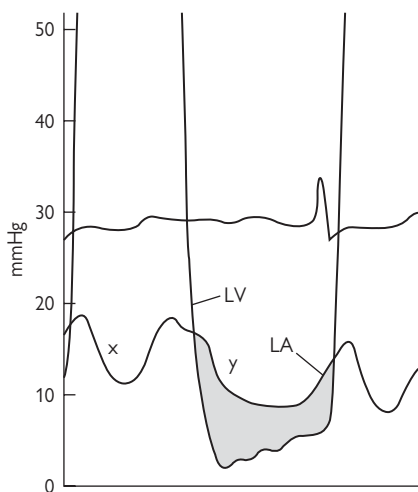


Fig. 6.11 Simultaneous LV and PCWP tracing in mitral stenosis. Reproduced with permission from Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*, 5th ed. Philadelphia: WB Saunders.

Valve regurgitation

- The severity of aortic regurgitation can be estimated by performing an aortogram. In severe aortic regurgitation, the LV is seen to opacify within one or two beats after contrast injection.
- Mitral regurgitation may be assessed by left ventriculography, with contrast seen to opacify the left atrium and pulmonary veins in severe regurgitation. In addition, mitral regurgitation (MR) may be associated with a prominent 'v' wave in the pulmonary capillary wedge tracing.

Intravascular ultrasound (Figs. 6.12 and 6.13)

Intravascular ultrasonography (IVUS) is a technology that allows direct visualization of atherosclerotic plaque and the vessel lumen, with recent advances allowing the echogenic characteristics of an IVUS image to give insights into the underlying histology. Ultrasound images are produced by passing an electrical current through a piezoelectric crystal that expands and contracts to produce sound waves when electrically stimulated. These sound waves are reflected from tissues, and return to the transducer, where they are detected and converted to an electrical impulse that can be presented graphically. A phased array of crystals (usually 64) is used, and these are sequentially activated to produce circumferential imaging. The equipment required to perform an IVUS examination involves a miniaturized ultrasound transducer mounted on a catheter (usually 2.6–3.5 Fr gauge), and computer interface that carries out image reconstruction.

Examination technique

- Intracoronary isosorbide dinitrate and IV heparin should be administered.
- The IVUS catheter should be carefully advanced distal to the area of interest.
- A motorized pullback device is then used to draw the IVUS catheter proximally at a fixed speed.
- Landmarks such as side branches can be useful, and positions may also be recorded angiographically.

Advantages of ultrasound

- The full circumference of the vessel wall is seen, not just two surfaces as in angiography, and is thus the method of choice to determine vessel luminal area.
- It is useful in imaging ambiguous lesions such as:
 - intermediate lesions of unknown severity
 - ostial stenosis
 - left main stem disease
 - disease at bifurcation sites.
- It images the plaque, not just the lumen.
- It allows optimal results during angioplasty and stenting.

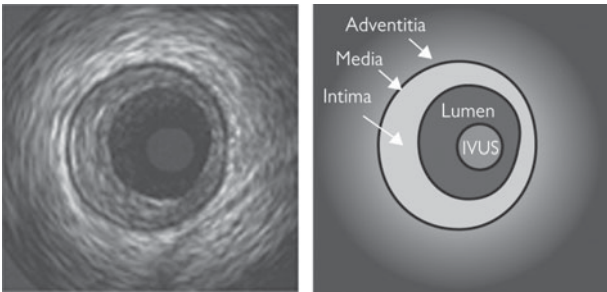


Fig. 6.12 Example of image obtained by IVUS.

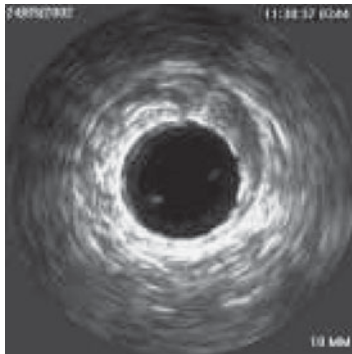


Fig. 6.13 IVUS image of a coronary stent.

Angioplasty and coronary stenting

- Currently, coronary stents are implanted in >85% of revascularization procedures in the UK.
- National Institute for Health and Clinical Excellence (NICE) guidelines state that 'stents should be used routinely for people with either stable or unstable angina or with acute myocardial infarction undergoing percutaneous intervention'.

Angioplasty

Before stents became widely used in the mid to late 1990s, balloon angioplasty alone was the commonest percutaneous treatment for coronary artery narrowings. The two main designs of balloon catheters now commonly used are over-the-wire and rapid-exchange systems. Both types of catheter consists of three parts:

- *the shaft*: there are two main varieties:
 - the hypotube, the advantage of which is a better balance between pushability and flexibility
 - the corewire design, which is superior in terms of flexibility
- *the lumen*: coaxial design (a tube within a tube) is the most common
- *the balloon*: these are constructed from varying plastics (e.g polyethylene, nylon), the mix of which affects the balloon's compliance. The design of the tip is important, as tapered tips are less traumatic when crossing narrowings. The balloon may also have a hydrophilic coating to render it more lubricious.

'Plain old balloon angioplasty' (POBA) remains indicated in the treatment of some coronary artery narrowings, particularly small vessels, vein grafts, and bifurcation side branches, in which the benefit of stenting has not been clearly demonstrated.

Coronary stenting

The primary function of a stent is to act as a scaffold to maintain vessel patency, and thus much of the success of stents is primarily due to their mechanical ability to produce large acute gains in lumen dimensions. Stents can be made of stainless steel, cobalt-based alloy, tantalum, nitinol, or polymer; however, the majority of stents used today are stainless steel and balloon mounted. Many designs have been experimented with, in an attempt to obtain an ideal balance of flexibility and radial strength, with flexibility allowing the stent to be positioned easily, and radial strength necessary for the scaffold function of the stent.

Angioplasty procedure (Fig. 6.14)

- Consent the patient.
- Cannulate the artery with the chosen guiding catheter. Ideally, the guiding catheter should be coaxial with the coronary ostium (thus allowing maximum support, and minimizing trauma to the vessel).
- A steerable 0.014" guide wire is introduced to the catheter via the haemostatic valve. The tip of the guide wire may be pre-shaped; however, many operators prefer to take a straight guide wire and shape the tip by hand.
- Using X-ray screening, and contrast to delineate the coronary anatomy, the guide wire is advanced along the vessel, beyond the narrowing, and placed as distally as possible in the vessel.
- An appropriately sized balloon is then chosen; the guiding catheter can be used as a reference when sizing the vessel. For calcific lesions and in-stent restenosis, shorter balloons with more highly rated burst pressure may be better.
- The balloon is now advanced along the guide wire to the correct position. In some situations, it will prove difficult to pass the balloon to the desired position, and in these instances deeper insertion of the guide catheter, or a more supportive guide catheter may be needed.
- Radio-opaque markers are used to position the balloon accurately. Inflation should be undertaken under X-ray screening, to ensure that the balloon does not move.

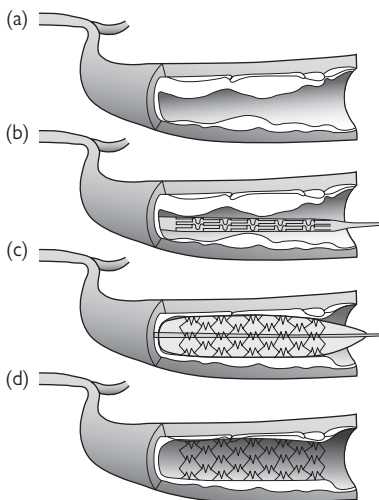


Fig. 6.14 Coronary stenting: a guide wire is introduced across the stastic segment of artery (a) and is used to position the stent (b). The stent is deployed by inflating the balloon (c). The balloon and guide wire are removed, leaving the stent in place (d).

Restenosis following percutaneous transluminal coronary angioplasty (PTCA)

Pathophysiology

The restenotic process consists of a series of complex events:

- vessel injury leads to platelet activation and *local thrombosis*.
- an *inflammatory reaction* is invoked, with neutrophil, monocyte, and lymphocyte migration to the site of injury.
- *smooth muscle proliferation* is driven by activated platelets and inflammatory mediators.
- finally, negative remodelling can occur.
- these processes occur at different rates, and may occur to different degrees depending upon the nature of vessel injury, and individual patient characteristics.

The problem

Large randomized trials have established that, following percutaneous intervention, restenosis rates in the treated vessel are between 30% and 60% (following angioplasty) and 15–30% (following stent implantation), and higher still in selected high-risk patients (e.g. those with diabetes). This relatively high incidence of *angiographic* restenosis, however, translates into revascularization in about 10% of patients, in whom *clinical* restenosis is said to have occurred.

Prevention of restenosis

Mechanical

Stent implantation

- Stent implantation reduces restenosis rates by increasing the mean luminal diameter after angioplasty, and preventing elastic recoil and adventitial constriction.

Optimization of stent deployment by IVUS guidance

- Using intravascular ultrasound to establish whether a stent has been adequately deployed improves the results of percutaneous intervention.

Pharmacological

Studies examining pharmacological interventions for reduction of restenosis have been disappointing.

Antithrombotic and antiplatelet treatment

Early aggressive antithrombotic and antiplatelet therapy using heparin, aspirin, GPIIb/IIIa antagonists, and clopidogrel reduce the incidence of acute stent thrombosis.

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Drug-eluting stents

Implantation of stents has, to a great extent, overcome the problem of elastic recoil and negative remodelling following PTCA. It is thus evident that neointimal proliferation, resulting in stent restenosis, remains the major limiting factor for stenting procedures. Much research has focused on the role of anti-proliferative agents in the reduction of restenosis, and recently drug-eluting stents (DESs) have emerged as the pre-eminent solution to this problem. Drug-eluting stents are coated stents, capable of releasing bioactive components into the local tissue and bloodstream. The advent of stents as a platform for the delivery of drugs, with subsequent reduction in rates of stent restenosis, is radically changing the treatment of patients with coronary artery disease. The number of CABG procedures performed worldwide is falling, with increasing numbers of patients, who previously would only have been candidates for CABG, being treated by percutaneous coronary intervention (PCI). Increasingly the favourable results obtained with DESs mean that PCI is performed in 'complex' cases such as left main coronary artery (LMCA) stenosis, diffuse disease, and bifurcation anatomy.

The latest randomized controlled trial evidence shows rates of target lesion revascularization (TLR) at 1 year for procedures carried out with DESs were less than 5%, compared to 10–25% for procedures that used a bare metal stent (BMS). This benefit appears to be maintained for up to 3 years in long-term follow-up studies.

No statistically significant differences in rates of mortality or acute myocardial infarction (MI) have been shown between DES types, although TLR rates for the Cypher™ sirolimus-eluting stent (SES) up to 9 months were statistically superior to the Taxus™ paclitaxel-eluting stent (PES).

In addition to development of DESs, advances in the platform itself such as design, material, and strut thickness also help combat restenosis rates. Reducing the quantity of metal results in less wall injury.

The 'holy grail' of coronary stent technology is a 'bio-absorbable' stent that will be completely absorbed over time, while maintaining vessel patency by altering arterial geometry at the time of implantation. Such stents are now in development, and phase two human trials have shown promising results in terms of reduction in plaque, zero stent thrombosis, and no major cardiac events up to 2 years of follow-up in small numbers of patients. Furthermore, studies show successful absorption of the stent and restoration of vasomotion—the ability of the coronary artery to contract and expand with normal pre-stent flexibility.

Those patients at higher risk of restenosis who require stent insertion (small-calibre arteries, longer atherosclerotic lesions, those with diabetes, saphenous vein grafts, chronic total occlusions (CTOs)) should have the use of DES considered.

Latest NICE guidance (2008) on the use of DESs has recommended their use if the target artery to be treated has less than a 3 mm calibre, or the lesion is longer than 15 mm. In real-world practice, this translates to coronary artery lesions in approximately 60–70% of patients undergoing PCI.

Drug-eluting stents

- Similarities between tumor growth and benign neointimal proliferation introduced the concept that immunosuppressant and cytotoxic agents might be beneficial for preventing in-stent restenosis (ISR).
- Incorporating these agents into stent coatings, using a number of techniques, has now enabled delivery of the active agent directly to its site of action, while limiting systemic side-effects.
- Crucially, the coatings allow sustained release of the agent, such that the therapy is present at the time that the target mechanism is physiologically active.
- The commonly used agents are sirolimus, which has a cytostatic action, and paclitaxel, which is cytotoxic.

Stent thrombosis

Recent concerns of higher rates of acute stent thrombosis following discontinuation of clopidogrel in DES patients prompted further investigation. Delayed endothelialization maintains a stent material substrate upon which thrombus formation can occur following the withdrawal of antiplatelet drugs.

It has since been concluded that the absence of a significant increase in associated death rates or MI as a result of stent thrombosis should not preclude their use within current guidelines. Premature discontinuation of dual antiplatelet therapy is a very definite risk for stent thrombosis, and an assessment of ability to comply with this must be made prior to stent implantation. Particular attention should be paid to bleeding risk and planned operative procedures.

The debate of duration of dual antiplatelet therapy continues; currently we recommend 12 months (as for non-ST-segment elevation MI) (NSTEMI), but some evidence suggests that the background, low rate of stent thrombosis continues in a linear manner until at least 3 years post implantation. Very late stent thrombosis rates (defined as thrombosis >1 year from implantation) require longer-term follow-up.

Current research has implied a relationship between the routine use of proton pump inhibitors (PPIs) and clopidogrel resistance, leading to the potential for increased risk of acute stent thrombosis. While this relationship is not yet fully understood, current recommendations are review of the clinical need for acid-suppression therapy and use of histamine-receptor-blocking agents as an alternative to PPIs if required.

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Physiological assessment of coronary flow

The shortcomings of coronary angiography in the *physiological* assessment of coronary stenosis are clear. Intravascular ultrasound can provide information on the size of the lumen and the composition of plaque, but again gives no information as to the effect that an atheromatous plaque may have on coronary flow. The knowledge as to whether a narrowing seen on angiography is the 'culprit' causing haemodynamic effects, and thus anginal symptoms, is valuable when guiding percutaneous intervention.

The fractional flow reserve (FFR) correlates distal coronary pressure to myocardial blood flow during maximum hyperaemia (induced by infusion of adenosine, or papaverine). FFR is defined as maximum myocardial blood flow in the presence of a stenosis divided by the theoretical maximum flow in the absence of a stenosis (see Fig. 6.15).

Thus, the information derived from FFR allows an 'on-the-spot' diagnosis as to what extent a given stenosis contributes to myocardial ischaemia (and angina), and can guide decisions regarding revascularization. At present, the best-established indication for coronary FFR estimation is as a diagnostic tool to assess 'severe' coronary narrowings, and for this it is extremely sensitive when used with a cut-off point of 0.75. The technique has also been used to optimize the results of stent implantation.

Two technologies are currently available that provide haemodynamic information derived from FFR calculations; these are pressure wires (which consist of a pressure transducer mounted on a 0.014" guide wire), and Doppler flow wires (which examine coronary flow velocities using spectral analysis).

Pressure wire

(e.g. The PressureWire™ (Radi Medical Systems))

- The pressure transducer is located at the transition between the radio-opaque wire tip, and the non-radio-opaque stem.
- The analyser shows simultaneous aortic and intracoronary pressure, as well as instantaneous FFR.

Doppler wire

(e.g. FlowWire™ (Endosonics))

- This obtains information on coronary flow velocity in the central area of the arterial lumen.
- Combining flow and electrocardiographic (ECG) information, it calculates systolic and diastolic components of flow velocity at baseline.
- Following induction of hyperaemia, the machine can calculate the coronary flow velocity reserve.

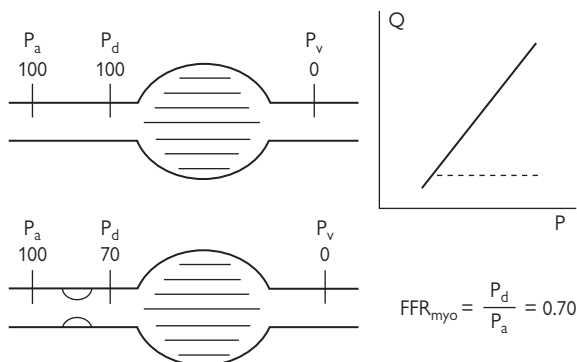


Fig. 6.15 During maximal arteriolar vasodilatation, the resistance of the myocardium is minimal, and so maximum myocardial blood flow is proportional to hyperaemic perfusion pressure. This equals $P_d - P_v$. As there is no decline in pressure along a normal coronary artery, and neglecting P_v , this implies that in a normal epicardial artery, perfusion pressure at hyperaemia equals P_a . In the presence of a stenosis, hyperaemic perfusion pressure decreases to P_d (after the stenosis). Thus, the maximum flow in the presence of a stenosis as a ratio (fraction) of normal maximum flow is represented by the ratio of perfusion pressures: P_d/P_a . This fraction of normal maximum flow, which is maintained despite the stenosis, is called the fractional flow reserve (FFR). Reproduced with permission from Pijls NH (2004). Optimum guidance of complex PCI by coronary pressure measurement. *Heart* **90**: 1085–93.

The FAME study

This randomized, prospective, multi-centre trial (FFR vs. Angiography for Multivessel Evaluation) looked at 1005 patients with multivessel coronary artery disease 12 months after receiving a stent, and compared outcomes for patients whose treatment was guided by FFR to those whose treatment was guided only by angiography.

It demonstrated a statistically significant 30% reduction in major adverse cardiac events (MACE) in the FFR arm, and also proved cost-effective with reduced need for repeat procedures. There was no difference in overall procedure time. Quality-of-life assessment (freedom from chest pain) for patients whose treatment was guided by FFR was equal to, and in some cases better than, that of patients whose treatment was based solely on angiography.


Primary angioplasty for STEMI

Pathophysiology

In the context of cardiac chest pain, ST-segment elevation on the 12-lead ECG usually signifies complete occlusion of a proximal epicardial coronary artery. This occurs as a result of rupture or erosion of a vulnerable atheromatous plaque, which leads to platelet activation and adhesion, formation of platelet-rich (white) thrombus, fibrin deposition, and red cell entrapment (forming red thrombus). If untreated, myocardial necrosis commences within 30 minutes, affecting full myocardial thickness within 6 hours; 40% of patients die before reaching hospital.

Treatment

Urgent restoration of coronary blood flow (reperfusion) prevents further LV damage and improves prognosis. The amount of myocardium that can be salvaged falls exponentially with time, with the greatest benefit within 3 hours following symptom onset, and little benefit after 12 hours.

Primary angioplasty is the preferred reperfusion strategy, where angiography can be performed within 90 minutes of presentation (see  STEMI: reperfusion by primary PCI, p. 268).

Patients can be transferred safely (by a trained ambulance crew with an advanced life support (ALS)-trained escort) from a district hospital to a cardiac centre for primary angioplasty.

Options for reperfusion

- **Primary angioplasty**
 - Immediate coronary arteriography and 'culprit' vessel angioplasty and stent implantation *without antecedent fibrinolysis*
 - Achieves full arterial patency (TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow) in 90–95%
 - Treats the occlusive thrombus and the culprit plaque
- **Intravenous fibrinolysis**
 - Immediate administration of a fibrinolytic agent (also called thrombolysis) without planned coronary arteriography
 - Achieves full arterial patency (TIMI grade 3 flow) in 50–60%
 - Contraindicated in up to 30% of patients
 - Does not treat the culprit plaque
- **Rescue angioplasty**
 - Urgent coronary arteriography 'culprit' vessel angioplasty and stent implantation performed when fibrinolysis has failed to achieve reperfusion (Persistent ST segment elevation \pm pain at 60–90 min)
- **Facilitated angioplasty**
 - Fibrinolysis prior to immediate coronary arteriography and 'culprit' vessel angioplasty and stent implantation

The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) study is a single-centre randomized trial involving >1000 patients, which compared stenting for acute STEMI with or without prior application of the Export™ Aspiration Catheter (Medtronic, USA). This is designed to suck out and capture thrombus from within an infarct-related artery, prior to bare-metal stenting.

Thrombus aspiration was associated with significantly improved myocardial reperfusion, as gauged by blush grade, compared with stenting with predilatation. The better reperfusion with aspiration was accompanied by significantly better resolution of ST-segment changes. MACE rates were similar between the groups at 30 days, but both end-points correlated significantly with blush grade and resolution of the ST-segment changes, independently of baseline clinical and angiographic features.

The finding strengthens the case for myocardial 'blush' grade as a predictor of clinical outcomes after PCI-treated acute MI, and advocates thrombus aspiration in the setting of acute STEMI.

In the context of primary percutaneous intervention for STEMI, the use of BMSs is currently recommended by NICE; however, there is emerging data that the use of DESs is safe in primary PCI, without increases in rates of ST, but with a reduction in the need for repeat revascularization.

Primary angioplasty: procedure

Indications

- Cardiac chest pain <12 hours
- ST elevation ≥ 1 mm in 2 contiguous leads
- Cardiogenic shock
- Able to consent
- NB: left bundle branch block (LBBB) and 'true posterior' MI are not clear indications for primary angioplasty, though in practice some centres do include these patients. Discuss immediately with the cardiology registrar.

Contraindications

- Suspected aortic dissection

Relative contraindications

- Active bleeding (antiplatelet therapy may have to be avoided, but may compromise outcome; these cases should be discussed directly with the operator).

Pre-procedure (work quickly—minutes matter)

- Consent
- The risk is higher than that of elective PCI. A procedural event rate of 5% (death, MI, stroke) should be quoted
- Full blood count (FBC), clotting, group and save, urea and electrolytes (U&E), creatine kinase (CK), troponin
- Analgesia + anti-emetic (diamorphine 5 mg; metoclopramide 10 mg)
- Oxygen if saturations <94%
- Aspirin 300 mg (chewed)
- Clopidogrel 600 mg
- Platelet glycoprotein GPIIb/IIIa receptor antagonist (abciximab) if no contraindication.

Procedure

- Access—femoral or radial. The femoral region should always be prepared in case of a need for transvenous pacing or intra-aortic balloon pump (IABP) insertion.
- A stent should be implanted where possible. Direct stenting without pre-dilatation may reduce the risk of distal embolization.
- The role of DESs in STEMI is undetermined.
- Platelet GPIIb/IIIa receptor antagonist if not already given.
- See also Fig. 6.16.

Additional considerations

- Culprit vessel PCI is prognostic. Other vessels may be treated to provide complete revascularization. However, complex non-culprit PCI should be avoided in most cases.
- Procedural success is defined by TIMI grade 2 or 3 flow with residual stenosis <20%.

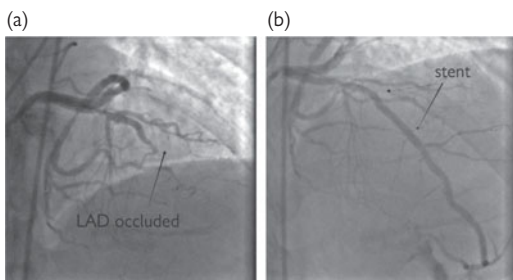


Fig. 6.16 Angiographic images from a 54-year-old male presenting with chest pain and anterior ST elevation. (a) The left anterior descending (LAD) artery is occluded mid vessel (arrow). (b) The same artery is now widely patent following primary angioplasty; A 3.5 × 24 mm bare metal stent has been implanted (arrow). The patient sustained minimal LV damage, and was discharged 48 hours later.

Further reading

- Keeley EC, Boura JA, Grines CL (2003). Primary angioplasty vs. intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. *Lancet* **361**: 13–20.
- Andersen HR, Nielsen TT, Rasmussen K, et al. (2003). A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* **349**: 733–42.
- Widimsky P, Budessinsky T, Vorac D, et al. (2003). Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial-PRAGUE-2. *Eur Heart J* **24**: 94–104.

Invasive assessment of vulnerable plaque

It has become apparent from intravascular ultrasound studies that non-obstructive and haemodynamically insignificant atherosclerotic plaques can be responsible for sudden death due to MI. These high-risk, or 'vulnerable' plaques are left untreated, as it is unclear which will progress to rupture. Angiography does not help differentiate between benign and hazardous plaques, and thus new technologies have been developed to assist in the identification of these plaques.

Histopathological correlates of vulnerable plaque

- Lipid-rich core
- Thin fibrous cap
- Necrotic core
- High degree of macrophage infiltration.

Intravascular ultrasound

- Able to discriminate plaques with low (lipid) and high (fibrous) echodensity
- Able to identify the capsule
- Able to identify areas of rupture within the plaque
- In combination with image analysis, information regarding the tissue types imaged can be derived, to provide a histological 'map' of the plaque.

Thermography catheters

- These catheters are able to detect the subtle temperature differences caused by inflammation that are present between stable and potentially unstable plaques.

Optical coherence tomography (OCT)

- This is similar in principle to intravascular ultrasound, but uses light instead of sound waves.
- The system has high axial resolution, down to 20 μm .
- At present, useful anatomical information can be obtained by this technique, but this is yet to be correlated with functional data.

Intravascular elastography

- This technology uses sound waves in a similar way to IVUS.
- Images are based on radial strain, and the system is therefore able to help differentiate soft from hard material.
- It is known that plaque rupture is often seen to occur in areas of increased strain, such as at the edge of plaques.

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Complex coronary angioplasty

Chronic total occlusion

A chronic total occlusion (CTO) is defined as a total coronary arterial occlusion known to be greater than 3 months old. Recent data suggest that nearly half of patients with significant coronary artery disease on a coronary angiogram have at least one CTO. Despite this high incidence, only about 10% of percutaneous interventions are performed for CTO, with the majority of patients being referred for coronary artery bypass graft surgery (CABG), which remains the 'gold standard' in CTO revascularization. The main reason that percutaneous interventions to CTOs fail is that a wire cannot be passed through the point of occlusion.

Why should we treat CTO?

- Relief of anginal symptoms
- Improved LV function
- Reduced need for CABG
- Successful intervention confers a survival advantage.

Who should treat CTO?

- Procedural success improves with operator experience. Lower-volume centres may wish to participate in CTO clubs and invite guest operators, and dedicated CTO days can be implemented at institutions committed to learning advanced CTO-PCI techniques.

The following factors have been shown to improve procedural success:

- experienced operator(s)
- specialist equipment such as 'CTO wires'
 - hydrophilic wires, can slip through the occlusion
 - tapered-tip guide wires: Cross-IT, Conquest, Miracle
 - 'heavy duty' wires with stiff tips, e.g. Confianza
 - procedural planning using non-invasive imaging such as multislice computed tomography (MSCT)
 - the use of micro-catheters to allow support of the wire and improve manipulation.

Predictors of procedural *failure* include:

- longer length of occlusion
- longer duration of occlusion
- presence of calcification
- presence of bridging collaterals
- 'blunt' (as opposed to tapered) stump at point of occlusion
- presence of a side branch at the point of occlusion
- vessel tortuosity.

What makes angioplasty complex?

- Increased risk of procedural failure
- Suboptimal result likely
- Complication rate higher
- Worse long-term outcome (death, MI, repeat procedure)

- Patient characteristics:
 - clinical presentation—acute vs. stable
 - diabetes
 - body habitus
 - significant co-morbidity
 - access problems—peripheral vascular disease
- Lesion characteristics: e.g. long, calcified, bifurcation, left main stem, chronic total occlusions
- Difficult anatomy.

Potential complications of CTO intervention

These procedures may be long, involve significant X-ray exposure, and considerable contrast load; thus, complications are not infrequent, and this must be considered when taking consent. Complications may include:

- impairment of collateral flow
- retrograde dissection
- perforation
- guide-wire entrapment
- subacute vessel reocclusion
- extensive contrast use, resulting in contrast-induced nephropathy
- increased radiation exposure.

The use of stents in CTO intervention

The implantation of a stent improves the outcome of CTO intervention when compared to balloon angioplasty alone. However, the long-term outcome of CTO intervention is hindered by a relatively high rate of restenosis. This has been somewhat ameliorated by the use of DESs, with improved efficacy of DESs demonstrated in several randomized controlled trials (RCTs).

Approaches to CTO percutaneous intervention

- A normal approach to CTO PCI involves a planned, progressive escalation in the equipment chosen to tackle the occlusion.
- A femoral approach, using 8 Fr guiding catheters is often chosen—such that guide catheter support can be optimized.
- Most operators will begin with softer wires, such that the occlusion may be 'probed'—before moving on to more stiff wires that may allow the cap of the occlusion to be penetrated. Over-the-wire balloons, and micro-catheters may increase the chances of successful wire penetration. If the occlusion is crossed, the occlusion can be dilated, and treated with stent implantation in a conventional manner.
- Several new wiring techniques and devices have evolved to treat CTO, further details on these can be found in the reference at the end of this section. These include:
 - side-branch technique Fig 6.17
 - parallel wire technique Fig 6.18
 - subintimal re-entry technique
 - IVUS-guided recanalization technique Fig. 6.19
 - retrograde approach
 - an approach that relies on access via collateral branches from the contralateral artery to gain access to the point of occlusion
 - 'see-saw' wiring technique.

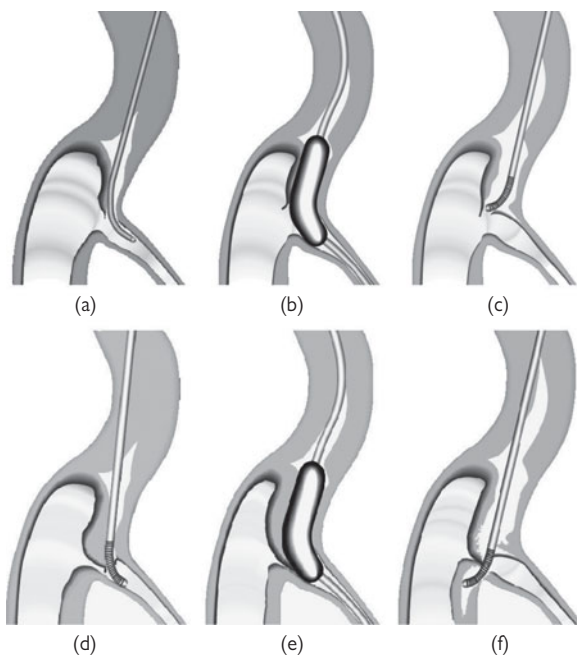


Fig. 6.17 Side-branch technique. Reproduced with permission from  www.summitmd.com.



Fig. 6.18 Parallel wire technique. Reproduced with permission from www.summitmd.com.

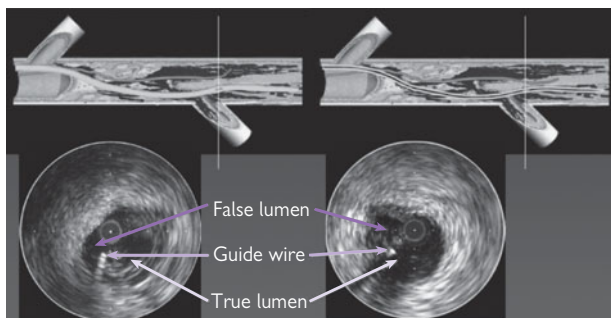


Fig. 6.19 IVUS-guided technique. Reproduced with permission from www.summitmd.com.

Adjunctive tools

- FrontRunner™ catheter
 - controlled blunt micro-dissection
- Optical coherence reflectometry (OCR) SafeSteer™ system
 - Forward-looking guidance system using OCR to determine tissue types (plaque vs. arterial wall) navigates through total occlusion
- Flow Cardia Crosser™ system
- High-frequency ultrasound recanalization
- Biological approach
- Prolonged pharmacological lysis infusion
- Collagenase plaque digestion.

Further reading

Further information on CTO treatment can be found in:

Di Mario C *et al.* (2007). European perspective in the recanalisation of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. *EuroInterv* 3: 30–43.

Bifurcation lesions

- The presence of atheromatous narrowings involving a coronary bifurcation present unique problems to the interventional cardiologist. As a subset of coronary artery narrowings, bifurcations are associated with higher rates of restenosis when compared to non-bifurcation lesions.
- A simple definition of bifurcation lesions can be the involvement of a side branch with a reference diameter greater than 2 mm in the stenosis. IVUS studies show that plaque in the main vessel almost invariably extends some distance into side branches that arise within the plaque. Furthermore, angioplasty to a plaque will often cause plaque-shift (the so-called 'snowplough' effect) into the daughter vessel.
- The Medina classification of bifurcation lesions, based on the presence or absence of atheroma in the proximal main branch, distal main branch and side branch, is shown in Fig. 6.20.
- Several strategies exist for the treatment of bifurcation lesions. These are broadly classified into single-stent (or provisional) techniques, and double-stent techniques. The majority of operators adopt a 'simple' provisional strategy, in which the main branch stent is implanted, and the side branch only treated in the event of its occlusion or dissection. The two-stent techniques have names such as 'T' stent, 'cullotte', 'crush', 'mini-crush', and 'shotgun', and are described in more detail in the reference at the end of this section.¹
- Unless flow in the side branch was severely impaired, or the ostium severely narrowed, during the treatment of the main vessel, a single-stent technique is preferable to the use of two stents. This is the so-called 'provisional T-stenting' technique.
- Dilating with a balloon through the stents of a strut carries the risk of deforming the distal parts of the stent and failure of adequate apposition of the stent to the vessel wall. This carries a high risk of thrombosis and restenosis, and thus a final 'kissing' balloon should be employed.

- Recent data regarding the use of a sirolimus-coated stent in the treatment of bifurcations suggests that implantation of a SES reduces the restenosis and reintervention rates after bifurcation lesion treatment.
- Poor results of bifurcation stenting have led to the development of dedicated bifurcation stents, although complexity of delivery has been a limiting factor. One example of a bifurcation stent that is currently undergoing investigation is the Tryton Stent™ (Tryton Medical, USA), which is a balloon-expandable side-branch-specific stent that can be wedged to any standard stent. The stent is initially deployed from the main vessel into the side branch, see Fig. 6.20.

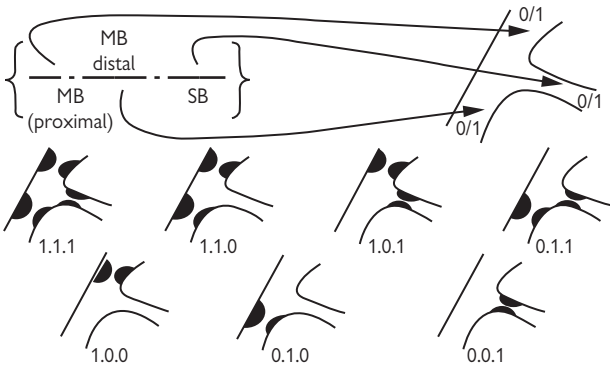



Fig. 6.20 The Medina classification, Reproduced with permission from Touch cardiology—see. <http://www.touchcardiology.com/articles/percutaneous-coronary-intervention-de-novo-bifurcation-lesions>.

Angioplasty in multivessel disease

Previous studies in the bare metal stent era showed PCI with BMS was inferior to CABG for multivessel disease (MVD) in terms of relieving angina and freedom from repeat procedures. Generally, these studies had included lower-risk patients with less complex disease and better LV function.

SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Coronary Surgery) is the largest prospective, randomized multicentre trial including 'all-comers' with complex MVD (left main stem/complex 3VD (three-vessel disease)). A total of 1800 patients from Europe and US were randomized to multivessel PCI with TAXUS™ DES or CABG, based on the revascularization strategy decision of a 'heart team', including an interventional cardiologist and surgeon. The only exclusion criteria were prior revascularization, acute MI, or need for concomitant cardiac surgery.

The SYNTAX scoring system was developed as a composite of established coronary disease risk-scoring systems and is now available as an online tool ( www.syntaxscore.com). It should be used to risk stratify patients and help decision making for complex revascularization cases.

- At one year there was an excess of repeat revascularizations in the PCI group (13.5% vs. 5.9%); however, rates of clinically significant graft or stent closure were remarkably similar.
- There was a statistically significant excess of strokes in the CABG group (2.2% vs. 0.6%).
- Overall MACE rates favour PCI for 'simple' MVD with less complex anatomy and CABG for complex or left main stem disease.

Left main stem (LMS) subgroup analysis

- There was no difference in all-cause deaths between PCI and CABG groups (4.2% vs. 4.4%) and MI (4.3% vs 4.1%).
- As before, there was an excess of strokes in the CABG group and reduction in repeat procedures. Longer-term results of LMS PCI are awaited.
- 2-year MACE rates remained significantly higher for PCI than CABG, mainly driven by higher repeat revascularization in the PCI arm.
- MACE rates at 2 years were not significantly different for patients with a low (0–22) or intermediate (23–32) baseline SYNTAX score treated with either PCI or CABG.
- For patients with high SYNTAX scores (≥ 33), MACE continued to be increased at 2 years in patients treated with PCI compared with CABG.
- In the predefined subgroups of patients with either 3VD or LM disease:
 - in the LM group, safety outcomes and MACE rates were similar for PCI and CABG, but the 2-year revascularization rate was lower in the CABG group
 - safety outcomes (death/CVA/MI) in the 3VD group were similar for PCI and CABG, but the 2-year revascularization and MACE rates favoured CABG.

SYNTAX score

Segments:		
RCA	RCA proximal	1
	RCA mid	2
	RCA distal	3
LM	Left main	5
LAD	LAD proximal	6
	LAD mid	7
	LAD apical	8
	First diagonal	9
	Add. first diagonal	9a
	Second diagonal	10
	Add. second diagonal	10a
LCX	Proximal circumflex	11
	Intermediate/anterolateral	12
	Obtuse marginal	12a
	Obtuse marginal	12b
	Distal circumflex	13
	Left posterolateral	14
	Left posterolateral	14a
	Left posterolateral	14b
	Posterior descending	15

Lesions are then graded depending on the presence of the following features, and a cumulative score derived:

- total occlusion
- trifurcation
- bifurcation
- severe tortuosity
- length >20 mm
- heavy calcification
- thrombus
- diffuse disease/small vessels.

Patients are classified as low (0–22), intermediate (23–32), or high (>33) risk, with a higher score favouring CABG.

Left main stem angioplasty

NICE guidelines had suggested that patients with stenosis of the LMCA should be offered bypass graft surgery. However, the emergence of registry data for both BMSs and, more recently, DESs has suggested that PCI to the LMS in patients with suitable LMS anatomy achieves acceptable results with low rates of procedural complication, and long-term vessel patency. The advent of DESs, and the reality of lower rates of in-stent restenosis compared to PCI with BMS, has further changed the approach of many interventional cardiologists to this previously taboo subset. In patients treated electively for LMS stenosis, reference vessel size and LV function appear to be the strongest predictors of favourable outcome.

Patient groups in whom LMS PCI may be appropriate

- Emergency LMS PCI:
 - bailout PCI after complications involving the LMS
- Elective LMS PCI:
 - patients refused CABG, but with continuing angina
 - patients who refuse surgery
 - younger patients with favourable LMS anatomy (i.e. not ostial disease, not short LMS).

Optimization of results of LMS PCI

Nothing less than an excellent angiographic result should be accepted. Intravascular ultrasound may be utilized both pre-procedure to ascertain the true vessel diameter, and post-procedure to ensure that stents have been adequately deployed.

LMS bifurcations may be approached using the techniques described before. There is emerging evidence that the use of DESs in the LMS bifurcation results in improved clinical outcomes.

Most operators routinely re-examine the LMS by angiography 2–4 months after PCI, to look for restenosis.

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Adjunctive therapy for angioplasty and stenting

Aspirin

The beneficial effect of aspirin during PCI has been shown in the Montreal Heart Study, in which treatment with aspirin and dipyridamole was superior to placebo in the prevention of peri-procedural Q-wave MI. Subsequent studies showed that dipyridamole added nothing to the beneficial effects provided by aspirin. Low-dose aspirin (usually 75 mg once daily), initiated at least 24 h prior to procedure, is recommended in patients undergoing PCI.

Thienopyridines

Clopidogrel and ticlopidine are thienopyridine derivatives that inhibit platelet function independently of aspirin, by interference with the platelet adenosine diphosphate (ADP) receptor. Early studies showed that a dual antiplatelet therapy with aspirin and ticlopidine was superior to aspirin alone. The use of ticlopidine was limited by potentially severe neutropenia. Clopidogrel, a newer thienopyridine, has a safer side-effect profile, and has thus become the agent of choice. The PCI-CURE (PCI—Clopidogrel in Unstable Angina to prevent Recurrent Events) study showed that pre-treatment with clopidogrel (300 mg loading dose, followed by 75 mg daily) in addition to aspirin for a median of 10 days before PCI, compared with aspirin alone, reduced the composite of cardiovascular death, MI, or urgent target vessel revascularization by 30% after 1 month. Most centres have adopted the policy of high-loading-dose clopidogrel (600 mg 2–4 hours pre-PCI) if the patient has not been preloaded.

Prasugrel is the newest oral antiplatelet agent to be reviewed by NICE. Its active metabolite binds irreversibly with the P2Y₁₂ class of ADP receptors on platelets. Data from TRITON TIMI 38 demonstrated that prasugrel therapy was associated with significantly reduced rates of ischaemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding in ACS patients treated with PCI. Overall mortality did not differ significantly between treatment groups. It has therefore been recommended for use in conjunction with aspirin for acute coronary syndrome (ACS) patients being treated with PCI in the following contexts:

- STEMI
- previous stent thrombosis with clopidogrel
- patient with diabetes.

After a loading dose of 60 mg, maintenance of 10 mg should be continued for one year.

Prasugrel should be used with caution in those at increased risk of bleeding, particularly those over 75 years, with a history of bleeding, or body weight <60 kg.

Heparin

Although there is general agreement that patients undergoing PCI should receive heparin before the intervention, there remains controversy regarding the issue of optimal heparin dosage. An inverse relation between the level of anticoagulation (measured by ACT) and the occurrence of acute ischaemic complications has been observed; however, longer ACTs are associated with higher bleeding risks. At present, an ACT >300 s is recommended for patients undergoing PCI. Low molecular weight heparin (LMWH, enoxaparin) has been shown to be effective in PCI; however, it has not as yet replaced unfractionated heparin (UFH) in routine use.

Glycoprotein IIb/IIIa inhibitors

The final common pathway for platelet aggregation is mediated by the platelet GPIIb/IIIa receptor. Trials in both diabetic and non-diabetic patients undergoing PTCA have found that the combination of stent and a GPIIb/IIIa inhibitor reduces cardiovascular morbidity and mortality compared with stent plus placebo.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor that exerts its activity by specifically and reversibly interacting with circulating (inactive) and clot-bound (active) thrombin. Clinical trials of bivalirudin in PCI have demonstrated similar benefits to the combination of abciximab and heparin, with a reduced risk of clinically significant blood loss.

NICE guidelines on use of GPIIb/IIIa inhibitors

'... it is recommended that a GP IIb/IIIa inhibitor is considered an adjunct to PCI to all patients with diabetes undergoing elective PCI, and for those patients undergoing complex procedures.'

'If PCI is indicated as part of the early management of unstable angina or NSTEMI, but is delayed beyond the early management phase, then the use of a IIb/IIIa inhibitor is recommended as an adjunct to PCI...'

Embolic protection devices

The distal embolization of particulate matter that lodges in the microcirculation (e.g. plaque debris, thrombus, and fibrin) during balloon inflation and stent deployment is becoming increasingly recognized as a cause of suboptimal results after PCI. Vein grafts, and thrombotic lesions are now recognized as being particularly prone to complications arising from distal embolization, such as the 'no-reflow' phenomenon, which is seen in up to 30% of vein grafts that contain thrombus at the time of PCI. Hence, the use of distal protection devices should be considered in these angioplasty subsets.

Devices for distal protection

Devices can be broadly split into those that occlude the conduit distally and then allow aspiration of debris, or distal filters that capture debris downstream.

Balloon occlusion devices (Fig. 6.21)

- *PercuSurge GuardWire*: this consists of three parts: (1) the GuardWire temporary occlusion catheter, which is placed distally in the vessel to allow occlusion; (2) the MicroSeal adapter that allows control over the inflation and deflation of the balloon; (3) the Export aspiration catheter, which allows collected debris to be aspirated into a 20 mL syringe.
- One of the main disadvantages of this system is that the target vessel is temporarily occluded, and thus the distal myocardium may be rendered ischaemic.

Filter devices

- *AngioGuard*: this device consists of an angioplasty guide wire with an expandable filter at the distal tip. The filter can be expanded once the target lesion has been crossed. Anterograde blood flow in the vessel is maintained, and displaced debris should theoretically be collected in the filter. The filter is then collapsed and withdrawn into the retrieving catheter.
- *FilterWireEX* (Fig. 6.22): this device consists of a 'fishmouth' opening distal filter, mounted on an angioplasty guide wire. The 'mouth' of the filter in theory expands to fill the entire lumen of the vessel. The filter is deployed by withdrawing a delivery sheath, and collected into a retrieval sheath.

Limitations of distal protection devices

- Crossing profile may cause distal embolization
- Incomplete filter apposition, or incomplete conduit occlusion
- Lack of protection of side branches
- Distal ischaemia in balloon occlusion devices.



Fig. 6.21 Balloon occlusion device for distal protection.



Fig. 6.22 Filterwire. Reproduced with permission from Boston Scientific.

Special techniques

Complex lesions that are unsuitable for routine angioplasty continue to pose a significant problem. A number of alternative devices have been developed, in an attempt to facilitate treatment of resistant stenoses, including laser, rotational, and directional atherectomy catheters and cutting balloons. A number of evolving clinical indications have been described in the clinical literature, including angioplasty-resistant stenoses (particularly heavily calcified lesions), in-stent restenosis, ostial lesions, and small-vessel disease.

Rotational atherectomy (rotablation)

Rotational atherectomy catheters have irrigated diamond-tipped burrs that rotate at up to 200 000 rpm and preferentially remove hard tissue, thus preparing a lesion for subsequent stenting. When conventional PCI is feasible, rotablation confers no additional benefits, and is associated with a higher risk of vessel dissection and perforation, spasm, and occlusion. It does, however, have a role in the management of some complex coronary lesions but is limited by cost and technical complexity, meaning additional operator and assistant training is required.

Cutting balloon

Cutting balloons are similar to conventional angioplasty balloons with the addition of three (2.0 and 2.5 mm balloon) or four (≥ 3.0 mm balloon) atherotomes, which are microsurgical blades, 0.010" in height, and bonded longitudinally to the balloon surface. The balloon is folded to shield the blades and protect the vessel wall as the catheter is passed to and from the lesion. As the cutting balloon is inflated, the atherotomes expand radially and incise the plaque, facilitating maximum dilatation of the target lesion with the least amount of force, and resulting in controlled injury, in contrast to the irregular and unpredictable intimal injury associated with regular balloon angioplasty. Additional care must be taken to avoid dissection and vessel occlusion.

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Mitral valvuloplasty (Fig. 6.23)

In carefully selected patients with mitral stenosis, percutaneous balloon mitral valvuloplasty (PMV) is now the treatment of choice. In fact the American Heart Association and American College of Cardiology states:

'In centers with skilled, experienced operators, PMV should be considered the initial procedure of choice for symptomatic patients with moderate to severe mitral stenosis who have favourable valve morphology in the absence of significant mitral regurgitation or left atrial thrombus. In asymptomatic patients with favourable valve morphology, PMV may be considered if there is evidence of a haemodynamic effect on left atrial pressure (new-onset atrial fibrillation) or pulmonary circulation (pulmonary artery pressure >50 mmHg at rest or 60 mmHg with exercise).'

Case selection

Careful case selection is paramount. The factors that must be considered include:

- **age:** older patients seem to have poorer outcomes in PMV. However, this is likely to be related to valve morphology in this group as opposed to age *per se*. In patients in whom surgery to the mitral valve is contraindicated, e.g. extreme age, and significant co-morbidity), adequate results can be obtained even in the presence of suboptimal valve morphology.
- **valve morphology:** a valve scoring system (ECHO based) is used to assess the valve's suitability for PMV. Studies have shown that patients with a valve score of less than or equal to eight consistently achieve superior and more sustained results from the procedure than patients with scores above eight.
- **mitral regurgitation:** the presence of significant mitral regurgitation is a contraindication to PMV.
- **left atrial thrombus:** this is a contraindication to PMV. Patients in AF should have been fully anticoagulated for a period of 4–6 weeks prior to the procedure.
- **pregnancy:** PMV can be performed in pregnancy. Radiation risk to the fetus is reduced after 14 weeks.

Complications of mitral valvuloplasty

- Mitral regurgitation
- Pericardial tamponade
- Thromboembolic events
- Iatrogenic ASD.

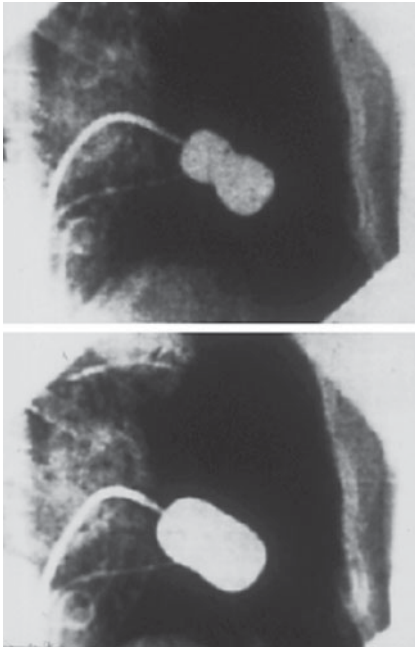


Fig. 6.23 Balloon mitral valvuloplasty: the upper panel shows the balloon partly inflated across the mitral valve, demonstrating the typical dumb-bell shape. As the inflation pressure and volume are increased, the stenosed valve dilates (lower panel). Adapted with permission from Braunwald E (ed) (2001). *Heart disease: a textbook of cardiovascular medicine*. 5th ed. WB Saunders: Philadelphia.

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Heart failure

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Introduction

Definition

Heart failure is a complex clinical syndrome in which the heart fails to meet the metabolic demands of the body. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. A diagnosis of heart failure is based on the presence of a triad of typical symptoms (shortness of breath on exertion and at rest, fatigue), signs (tachycardia, tachypnoea, raised jugular venous pressure, peripheral oedema, and pulmonary congestion), and objective evidence of a structural or functional cardiac abnormality (cardiomegaly, abnormal echocardiogram, raised natriuretic peptide concentration). A clinical response to treatment directed at heart failure alone (e.g. diuretic use) may be a useful adjunct but is not sufficient to establish the diagnosis.

Epidemiology and prognosis

Heart failure is the fastest-growing cardiovascular disease, affecting 2–3% of the overall population. The prevalence rises with age, affecting between 10% and 20% of the population aged over 70 years. Although recent epidemiological studies indicate improved survival, the overall prognosis remains poor, with mortality exceeding 50% at 5 years. The primary causes of death are either progressive pump failure or sudden cardiac death secondary to ventricular arrhythmia. Morbidity also remains poor, with a high rate of rehospitalization (up to 50% in a year), placing a significant burden on national healthcare systems.

Pathophysiology

The origin of symptoms in heart failure is poorly understood. An initial event (infarction, inflammation, pressure/volume overload) causes myocardial damage, resulting in an increase in myocardial wall stress. This is followed by the activation of multiple neuroendocrine systems including the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the release of cytokines such as tumour necrosis factor (TNF). Neuroendocrine activation is also accompanied by structural and metabolic changes in the peripheral skeletal muscle and by abnormalities in cardiopulmonary reflex function such as the baroreflex and chemoreflex. These produce further wall stress, perpetuating this vicious cycle (see Fig. 7.1).

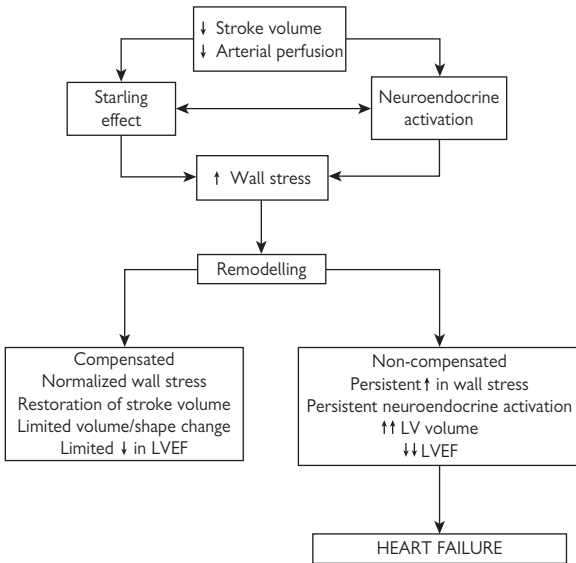



Fig. 7.1 Pathophysiology of heart failure. LV = left ventricle; LVEF = left ventricular ejection fraction.

Forms of heart failure

Acute vs. chronic heart failure

The clinical manifestations depend on the speed with which the syndrome develops. Acute heart failure is often used to describe the patient with acute-onset dyspnoea and pulmonary oedema, but can also apply to cardiogenic shock where the patient is hypotensive and oliguric. Compensatory mechanisms have not yet become operative. Acute deterioration may be a consequence of myocardial infarction (MI), arrhythmia, or acute valve dysfunction (e.g. endocarditis). See  Acute pulmonary oedema: assessment, p. 724.

Systolic vs. diastolic heart failure

Most patients with heart failure have evidence of both systolic (failure of the ventricle to eject blood) and diastolic (failure of the ventricle to relax and fill with blood) dysfunction. Patients with diastolic heart failure have symptoms and signs of heart failure with a preserved LVEF. Current studies indicate that more than 50% of heart failure patients have a normal or near-normal ejection fraction (EF), and their prognosis appears to be similar to that of those with systolic heart failure. The terms diastolic heart failure, heart failure with normal ejection fraction (HFNEF), and heart failure with preserved ejection fraction are used interchangeably.

Right vs. left heart failure

Right and left heart failure refers to whether the patient has either predominantly systemic venous congestion (swollen ankles, hepatomegaly) or pulmonary venous congestion (pulmonary oedema). These terms do not necessarily indicate which ventricle is most seriously affected.

Fluid retention in heart failure is due to a combination of factors: reduced glomerular filtration rate (GFR), and activation of the renin–angiotensin–aldosterone system, and sympathetic system. However, remember there are causes for swollen ankles other than heart failure (gravitational disorder, e.g. immobility, venous thrombosis or obstruction, varicose veins, hypoproteinaemia, e.g. nephrotic syndrome or liver disease, lymphatic obstruction).

High-output vs. low-output heart failure

A variety of high-output states may lead to heart failure, e.g. thyrotoxicosis, Paget's disease, beri-beri, and anaemia. This is characterized by warm extremities and normal or widened pulse pressure. The arterial–mixed venous oxygen saturation (a marker of the ability of the heart to deliver oxygen to the metabolizing tissues) is typically normal or even low in high-output heart failure. In contrast, low-output states are characterized by cool pale extremities, cyanosis due to systemic vasoconstriction, and low pulse volume. The arterial–mixed venous oxygen saturation is typically abnormally high in low-output states.

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Causes and precipitants

In all patients with heart failure, it is important to carefully consider the underlying aetiology, as there may be specific exacerbating factors or other diseases that influence the patients' management. A non-exhaustive list is given below.

Aetiology of heart failure

- Ischaemic heart disease (accounting for 70% of patients with heart failure in the developed world)
- Idiopathic dilated cardiomyopathy (unknown aetiology, up to 50% may be familial)
- Valve disease (accounting for 10% of patients with heart failure)
- Hypertension (the primary cause of heart failure in patients of African-Caribbean descent)
- Alcoholic cardiomyopathy
- Post viral
- Peripartum cardiomyopathy
- Infiltrative disease (amyloidosis, sarcoidosis)
- Connective tissue disease
- Iatrogenic (chemotherapy, radiotherapy)
- Infections (Chagas' disease, human immunodeficiency virus (HIV))
- Thyroid disease (severe hypo- or hyperthyroidism)
- Haemochromatosis
- Nutritional (beri-beri)

Patients with compensated heart failure have a high rate of readmission to hospital with acute exacerbations. A number of studies have demonstrated that a precipitating cause for emergency admission to hospital with heart failure can be identified in up to two-thirds of patients.

- *Inappropriate reduction in therapy*: self-discontinuation or iatrogenic withdrawal of diuretics, angiotensin-converting enzyme inhibitor (ACE-I), digoxin, as well as dietary excess of salt are recognized precipitants. Education of the patient/family is important.
- *Cardiac arrhythmias*: most commonly atrial fibrillation (AF), but any tachyarrhythmia will further reduce LV filling and stroke volume, and may exacerbate ischaemia. Marked bradycardia reduces cardiac output, especially if stroke volume cannot increase any further.
- *Myocardial ischaemia or infarction*: exacerbates LV dysfunction, and may worsen mitral regurgitation (MR) due to ischaemia of papillary muscles.
- *Infection*: respiratory infections are more common, but any systemic sepsis can precipitate heart failure due to a combination of factors such as direct myocardial depression from inflammatory cytokines, sinus tachycardia, fever, etc.
- *Anaemia*: this causes a high-output state that may precipitate acute heart failure, and may exacerbate underlying ischaemia.
- *Concomitant drug therapy*: drugs that directly depress myocardial function (e.g. calcium antagonists—verapamil, diltiazem; many antiarrhythmics, anaesthetics, over-enthusiastic initiation of β -blockers, etc.), as well as drugs causing salt and water retention (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oestrogens, steroids, COX-2 antagonists) may precipitate heart failure.

- **Alcohol:** this is directly toxic and, in excess, can depress myocardial function as well as predispose to arrhythmias.
- **Pulmonary embolism:** the risk increases in the immobile patient with low-output state and AF.

It is very important to look for precipitating causes in all patients with heart failure. Once the precipitant has been identified and treated, appropriate measures (patient and family/education, adjustment of therapy, etc) should be put into place to prevent recurrence. See Table 7.1.

Table 7.1 Population-attributable risk of heart failure related to various risk factors^a

Risk factor	Attributable risk (%)
Coronary disease	61.6
Cigarette smoking	17.1
Hypertension	10.1
Physical inactivity	9.2
Male sex	8.9
<High school education	8.9
Overweight	8.0
Diabetes	3.1
Valvular heart disease	2.2

^aHe, J, Ogden LG, Bazzano LA, et al (2001). Risk factors for congestive heart failure in US men and women: NHANES 1 Epidemiologic follow-up study. *Arch Intern Med* **161**: 996.

Conditions mimicking heart failure

- Obesity
- Chest disease—including lung, diaphragm, or chest wall
- Venous insufficiency in lower limbs.
- Drug-induced ankle swelling (e.g. dihydropyridine calcium blockers)
- Drug-induced fluid retention (e.g. NSAIDs)
- Hypoalbuminaemia
- Intrinsic renal disease
- Intrinsic hepatic disease
- Pulmonary embolic disease
- Depression and/or anxiety disorders
- Severe anaemia
- Thyroid disease
- Bilateral renal artery stenosis

Signs and symptoms

The evaluation of a heart failure patient should start with a comprehensive history and clinical examination. Primary symptoms can be attributed to either reduced cardiac output or fluid accumulation, and include:

- fatigue
- dyspnoea (on exertion or at rest)
- orthopnoea
- paroxysmal nocturnal dyspnoea
- peripheral oedema
- chest pain
- palpitations (tachycardia)
- hypotension
- raised jugular venous pressure (JVP)
- displaced apex beat
- gallop rhythm (3rd heart sound)
- cahexia.

It is important to remember that heart failure is a multisystem disorder affecting every single aspect of a patient's body. It is not unusual for patients to present with:

- gastrointestinal symptoms secondary to congestive hepatomegaly, ascites, reduced bowel perfusion, and oedema (abdominal distension and pain, anorexia, bloating, nausea, constipation, jaundice)
- genitourinary symptoms secondary to impaired renal perfusion (oliguria/anuria, urinary frequency, nocturia)
- cerebrovascular symptoms secondary to cerebral hypoperfusion and associated electrolyte abnormalities (confusion, memory impairment, anxiety, headaches, insomnia, bad dreams or nightmares, psychosis with disorientation, delirium, or hallucinations)
- musculoskeletal symptoms (gout, carpal tunnel syndrome, muscle cramps).

Many of these signs can be difficult to elicit particularly in a noisy emergency or outpatient clinic. Even in study conditions, the reproducibility and inter-observer agreement of the presence of signs is low. Despite this, a clinical diagnosis of heart failure can be made with some certainty when multiple signs are present in the same patient (see Table 7.2).

Symptoms alone can be used to classify the severity of congestive heart failure (CHF) and to monitor the effect of treatment, although the link between symptoms and degree of LV dysfunction is weak. The New York Heart Association classification (NYHA) is widely used.

NYHA classification of heart failure

- Class I No limitation of physical activity.
- Class II Slight limitation of physical activity—symptoms with ordinary levels of exertion (e.g. walking up stairs).
- Class III Marked limitation of physical activity—symptoms with minimal levels of exertion (e.g. dressing).
- Class IV Symptoms at rest.

An alternative classification system of heart failure is the 'Stages of Heart Failure' proposed by the American College of Cardiology (ACC) and the American Heart Association (AHA). This classification system places particular emphasis on the progressive nature of the heart failure, and defines the appropriate therapeutic approach for each stage (see Table 7.2). Unlike the NYHA classification, this system is unidirectional and therefore cannot be used as a means of assessing the patient's response to treatment. See also Fig. 7.2.

Table 7.2 ACC/AHA stages of heart failure

Stage A	Stage B	Stage C	Stage D
At high risk for developing heart failure (HF) but without identified structural or functional heart disease, symptoms or signs of HF	Structural or functional heart disease but without symptoms or signs of HF	Structural or functional heart disease with current or prior symptoms or signs of HF	Refractory HF symptoms despite maximal medical therapy
e.g. patients with: hypertension, atherosclerosis, diabetes, obesity, metabolic syndrome	e.g. previous MI, left ventricular hypertrophy, reduced EF, valvular lesions	e.g. known structural heart disease with associated dyspnoea, fatigue, oedema	e.g. marked symptoms on minimal exertion or at rest, hospitalized patients

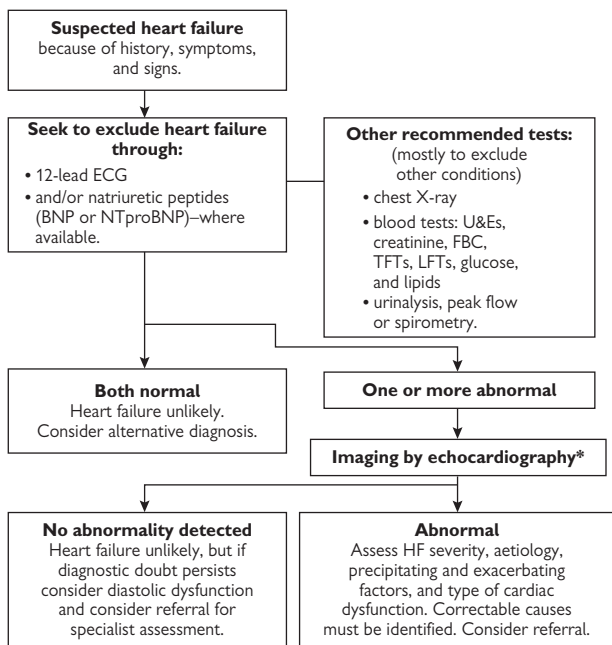


Fig. 7.2 Algorithm summarizing recommendations for the diagnosis of heart failure.

*Alternative methods of imaging the heart should be considered when a poor image is produced by transthoracic Doppler 2D-echocardiography—alternatives include transoesophageal echocardiography (TOE), radionuclide imaging, or cardiac magnetic resonance imaging (MRI).

BNP = B-type natriuretic peptide; ECG = electrocardiogram; FBC = full blood count; LFTs = liver function tests; NTproBNP = N-terminal pro-B-type natriuretic peptide; TFTs = thyroid function tests; U&Es = urea and electrolytes.

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Investigations

Investigations for all patients with heart failure

- **ECG:** although there are no specific changes in heart failure, a normal ECG is observed in only 2% of cases and should encourage the clinician to consider an alternative diagnosis in the absence of firm clinical signs. Common findings include: sinus tachycardia/bradycardia, arrhythmias, voltage criteria for left ventricular hypertrophy (LVH), evidence of current or past ischaemia/infarction, and conduction system defects.
- **Chest X-ray (CXR):** permits assessment of pulmonary congestion and may demonstrate other non-cardiac causes of dyspnoea. Common findings include: cardiomegaly, pulmonary congestion with alveolar oedema, prominent upper lobe vessels, 'bat's wings' and Kerley B lines and pleural effusions (see Fig. 7.3).
- **Echocardiography (ECHO):** this is the key investigation in patients with HF and is mandatory for confirming the diagnosis. Apart from documenting systolic and diastolic left ventricular function, the scan is useful in the identification of various causes or complications of heart failure (see Table 7.3). If an echocardiogram does not confirm a diagnosis of HF despite suggestive clinical symptoms and signs, consider an alternative diagnosis or a referral for a specialist review.
- **Natriuretic peptides:** evidence exists supporting the use of plasma concentrations of natriuretic peptides for diagnosing, staging, or even identifying patients at risk for clinical events. A normal plasma concentration in an untreated patient has a high negative predictive value, making HF an unlikely cause of symptoms.
- **Blood tests:** FBC, U&Es, LFTs, TFTs, glucose, uric acid.

Investigations to consider for selected patients with heart failure

- **Blood tests:** troponin I or T, iron studies, folate, vitamin B₁₂, autoimmune screen, immunoglobulins and protein electrophoresis, serum ACE
- **Viral titres**
- **Urine sample:** albumin/creatinine ratio, 24-hour urine collection for protein, catecholamines, Bence-Jones protein
- **Arterial blood gases**
- **Pulmonary function tests**
- **Exercise testing**
- **Ambulatory ECG monitoring** (QT dispersion, heart-rate variability)
- **Stress imaging**
- **Radionucleotide ventriculography**
- **Cardiac magnetic resonance**
- **Coronary angiography** (computed tomography (CT) or conventional)
- **Myocardial biopsy**
- **Right-heart catheterization.**

Table 7.3 Conditions predisposing to or complicating heart failure that may be identified by echocardiography

Echocardiographic findings	Examples of possible aetiology
Identification of anatomical defects	Atrial septal defect (ASD), ventricular septal defect (VSD)
Valvular pathology	Aortic valve or mitral valve stenosis or insufficiency
Pericardial disease	Acute or chronic pericarditis Constrictive pericarditis Pericardial effusion
Identification of regional ventricular wall motion abnormalities	Ischaemic heart disease
Altered myocardial architecture	Hypertrophic cardiomyopathy Infiltrative diseases (amyloidosis)
Estimation of pulmonary artery pressure	Pulmonary hypertension (cor pulmonale as a result of primary pulmonary hypertension or secondary to lung disease)
Identifying complications of reduced ventricular function	Intramural thrombus secondary to ventricular dilatation, reduced contraction, or aneurysm

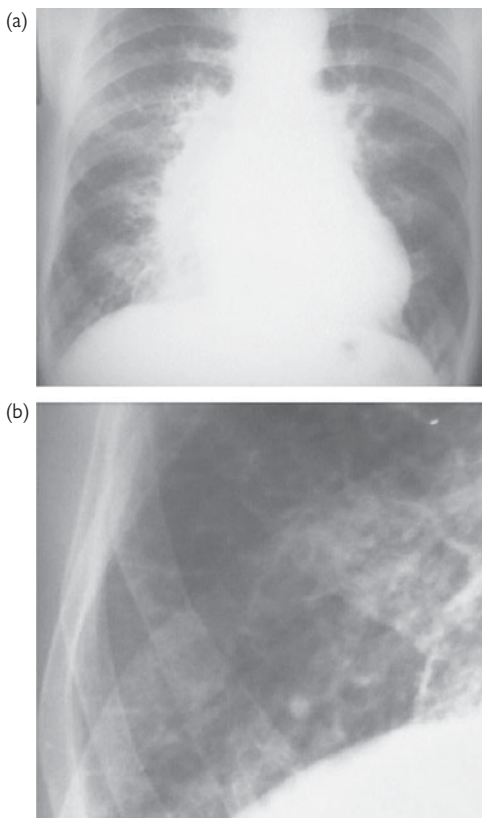


Fig. 7.3 CXR findings in heart failure. (a) There is cardiomegaly with prominent upper lobe vessels and alveolar oedema ('Bat's wing shadowing'); (b) magnification of the right costophrenic angle showing septal lines (Kerley B lines) due to interstitial oedema.

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Management of heart failure

Management outline in chronic heart failure

- Establish a firm diagnosis of HF
- Attempt to determine the aetiology and ascertain the severity of HF
- Correct precipitating or exacerbating factors
- Multidisciplinary approach to treatment (HF is a complex syndrome necessitating the involvement of a number of healthcare professionals in the community and secondary care including: general practitioner (GP), cardiologist, electrophysiologist, cardiac surgeon, heart failure nurse, cardiac rehabilitation team, dietician, psychologist, expert in sexual dysfunction)
- Education of the patient and relatives (see Table 7.4)
- Monitor progress and manage accordingly.

Objectives of treatment

- Reduce mortality
- Reduce morbidity (to improve quality of life by relieving symptoms, increasing exercise capacity, reducing the need for hospitalization and providing end-of-life care)
- Prevention (can be divided into two separate entities: (1) prevention of cardiovascular risk factors that may lead or contribute to the development of heart failure, i.e. hypertension, diabetes, obesity, and (2) prevention of progression of myocardial damage, remodelling, and reoccurrence of symptoms once HF is established).

Fig 7.4 summarizes a treatment algorithm for patients with symptomatic HF and reduced systolic function.

Table 7.4 Essential topics in patient education with associated skills and appropriate self-care behaviours

Educational topics	Skills and self-care behaviours
Definition and aetiology of heart failure	Understand the cause of heart failure and why symptoms occur
Symptoms and signs of heart failure	Monitor and recognize signs and symptoms Record daily weight and recognize rapid weight gain Know how and when to notify healthcare provider Use flexible diuretic therapy if appropriate
Pharmacological treatment	Understand indications, dosing, and effects of drugs Recognize the common side-effects of each drug
Risk-factor modification	Understand the importance of smoking cessation Monitor blood pressure if hypertensive Maintain good glucose control if patient has diabetes Avoid obesity
Diet recommendation	Sodium restriction if prescribed Avoid excessive fluid intake Modest intake of alcohol Monitor and prevent malnutrition

Table 7.4 (contd.)

Educational topics	Skills and self-care behaviours
Exercise recommendation	Be reassured, comfortable about physical activity Understand the benefits of exercise Perform exercise training regularly
Sexual activity	Discuss problems with healthcare professionals Be reassured about engaging in sexual intercourse and understand specific sexual problems and various coping strategies
Immunization	Receive immunization against infections such as influenza and pneumococcal disease
Sleep and breathing disorders	Recognize preventive behaviour such as reducing weight in obese, smoking cessation, abstinence from alcohol Learn about treatment options if appropriate
Adherence	Understand the importance of following treatment recommendations Maintain motivation to follow treatment plan
Psychosocial aspects	Understand that depressive symptoms and cognitive dysfunction are common in patients with HF, and the importance of social support Learn about treatment options if appropriate
Prognosis	Understand important prognostic factors and make realistic decisions Seek psychosocial support if appropriate

ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (2008).
Eur Heart J 29: 2388–2442.

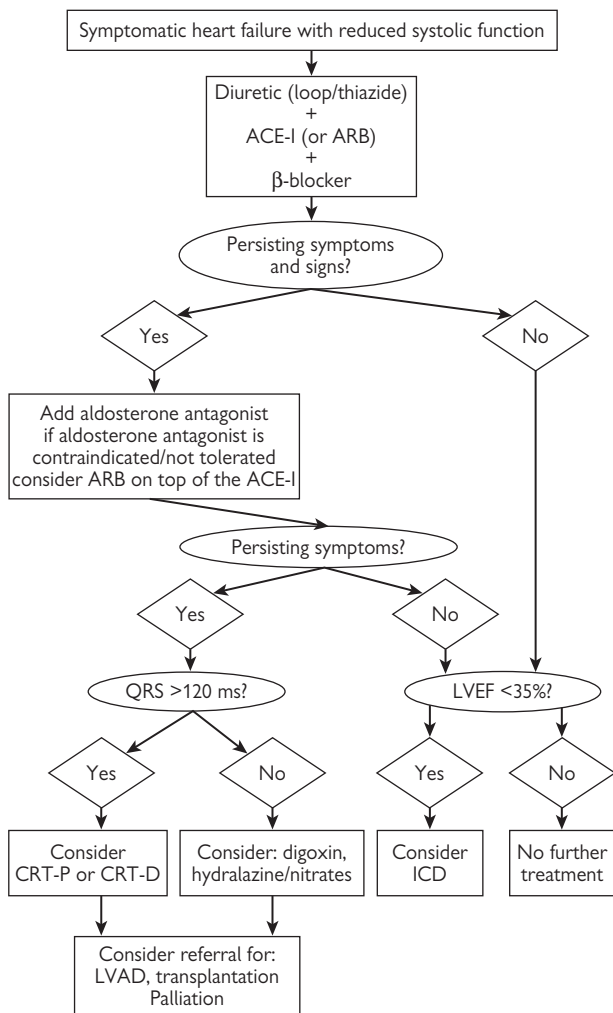


Fig. 7.4 Treatment algorithm for patients with symptomatic heart failure and reduced systolic function. Adapted from ESC (2008). Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **29**: 2388–2442 and NICE guidelines www.nice.org. ARB = angiotensin receptor blocker; LVAD = left ventricular assist device.

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Diuretics in heart failure

- Diuretics provide symptomatic relief from pulmonary and systemic congestion by reducing fluid overload.
- With the exception of aldosterone antagonists (spironolactone and eplerenone), diuretics do not offer any significant prognostic benefit.
- Loop diuretics cause more pronounced diuresis (and natriuresis), and are the option of choice in patients with moderate to severe heart failure.
- A thiazide may be used in combination with loop diuretics for resistant oedema. Regular monitoring is required to avoid dehydration, hyponatraemia, hypokalaemia, and hypomagnesaemia.
- Diuretics cause activation of the renin–angiotensin–aldosterone system and should be used in combination with an ACE-I/ARB when possible.
- Start with a low dose (especially in diuretic-naïve patients and the elderly) and increase the dose until clinical improvement occurs.
- Once fluid overload resolves, readjust the diuretic dose to avoid dehydration. Aim to maintain 'dry weight' with the lowest dose possible.
- Self-adjustment of the diuretic dose based on daily weight measurements and other clinical signs of fluid retention should be part of the patient education.
- It is essential to monitor potassium, sodium, and creatinine levels during diuretic therapy.

Practical considerations in the treatment of heart failure with loop diuretics

See Table 7.5.

Table 7.5 Considerations in the treatment of heart failure with loop diuretics

Problems	Suggested action
Hypokalaemia/ hypomagnesaemia	<ul style="list-style-type: none"> • Increase ACE-I/ARB dosage • Add aldosterone antagonist • Potassium supplements • Magnesium supplements
Hyponatraemia	<ul style="list-style-type: none"> • Fluid restriction • Stop thiazide diuretic or switch to loop diuretic • Reduce dose/stop loop diuretics if possible • Consider arginine vasopressin (AVP) antagonist if available • Intravenous (IV) inotropic support • Consider ultrafiltration
Hyperuricaemia/ Gout	<ul style="list-style-type: none"> • Consider allopurinol • For symptomatic gout use colchicine for pain relief • Avoid NSAIDs
Hypovolaemia/ dehydration	<ul style="list-style-type: none"> • Assess volume status • Consider reduction of diuretic dosage

Table 7.5 (contd.)

Problems	Suggested action
Insufficient response or diuretic resistance	<ul style="list-style-type: none"> ● Check compliance, fluid and salt intake ● Review other drugs (NSAIDs, steroids) ● Increase dose of diuretic ● Consider switching from furosemide to bumetanide or torasemide ● Add aldosterone antagonist ● Combine loop diuretic and thiazide/metolazone ● Administer loop diuretic twice daily or on empty stomach ● Consider short-term IV infusion of loop diuretic ● Consider low-dose dopamine infusion
Renal failure (excessive rise in urea and/or creatinine)	<ul style="list-style-type: none"> ● Check for hypovolaemia/dehydration ● Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim ● Withhold aldosterone antagonist ● If using concomitant loop and thiazide diuretic stop thiazide diuretic ● Consider reducing dose of ACE-I/ARB ● Consider ultrafiltration

Adapted from ESC (2008). Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **29**: 2388–2442.

Diuretic doses used in patients with heart failure

See Table 7.6.

Table 7.6 Diuretic doses used in patients with heart failure

Diuretics	Initial dose (mg)	Usual daily dose (mg)
Loop diuretics^a		
Furosemide	20–40	40–240
Bumetanide	0.5–1.0	1–5
Torsemide	5–10	10–20
Thiazides^b		
Bendroflumethiazide	2.5	2.5–10
Hydrochlorothiazide	25	25–100
Metolazone	2.5	2.5–10
Indapamide	2.5	2.5–5
Potassium-sparing diuretics^c		
Spironolactone/eplerenone	12.5–25	50
Amiloride	2.5	5–20
Triamterene	25	50

Adapted from ESC (2008). Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **29**: 2388–442.

^aHigher doses may be required in individuals with renal impairment; excessive doses however may cause renal impairment and ototoxicity.

^bDo not use thiazides if estimated GFR (eGFR) < 30 mL/min, except when prescribed synergistically with loop diuretics.

^cAldosterone antagonists should always be preferred to other potassium-sparing diuretics.

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Angiotensin-converting enzyme inhibitors for heart failure

Unless contraindicated or not tolerated, all patients with symptomatic HF or asymptomatic left ventricular dysfunction (LVEF \leq 40%) should receive an ACE-I

ACE-Is reduce mortality and morbidity (improve symptoms, exercise tolerance, and quality of life, and reduce the need for hospitalization) and improve or at least prevent further deterioration of ventricular function.

Contraindications

- History of angioedema
- Bilateral renal artery stenosis
- Serum potassium concentration >5 mmol/L
- Serum creatinine >220 μ mol/L
- Severe aortic valve stenosis.

Initiation of ACE inhibitors

- Check renal function and serum electrolytes.
- Start with a low dose and recheck renal function and serum electrolytes within 1–2 weeks of commencing the treatment.
- Consider dose up-titration at 2–4-week intervals and recheck renal function and serum electrolytes within 1–2 weeks of dose up-titration.
- More rapid dose up-titration can be carried out, but close supervision is required.
- Once a maintenance dose has been achieved, recheck renal function and serum electrolytes at 1, 3, 6 months, and 6 months thereafter.
- Aim for evidence-based target dose or the maximum tolerated dose.

Doses of ACE inhibitors used in heart failure

See Table 7.7.

Table 7.7 Doses of ACE-Is used in heart failure

Licensed ACE-I	Initiating dose (mg)	Target dose (mg)
Captopril	6.25 three times daily	50–100 three times daily
Cilazapril	0.5 once daily	1–2.5 once daily
Enalapril	2.5 once daily	10–20 twice daily
Fosinopril	10 once daily	40 once daily
Lisinopril	2.5–5.0 once daily	20–35 once daily
Perindopril	2.0 once daily	4 once daily
Quinapril	2.5 once daily	10–20 once daily
Ramipril	1.25 once daily	10 once daily (or 5 twice daily)
Trandolapril	0.5 once daily	4 once daily

Practical considerations in treatment of heart failure with ACE inhibitors

Deteriorating renal function

- Some rise in urea and creatinine is expected and should not cause concern.
- An increase of $\leq 50\%$ from baseline or to an absolute concentration of $265 \mu\text{mol/L}$, whichever is lower, is acceptable.
- Check for other nephrotoxic drugs (NSAIDs).
- If creatinine rises to $>265 \mu\text{mol/L}$ but is $<310 \mu\text{mol/L}$, halve the dose of ACE-I and monitor biochemistry closely.
- If creatinine rises to $\geq 310 \mu\text{mol/L}$, stop ACE-I and monitor biochemistry closely.

Hyperkalaemia

- Check for other drugs causing hyperkalaemia (potassium-sparing diuretics, supplements).
- If potassium rises to $>5.5 \text{ mmol/L}$, halve dose of ACE-I and monitor biochemistry.
- If potassium rises to $>6.0 \text{ mmol/L}$, stop ACE-I and monitor biochemistry.

Symptomatic hypotension

- Asymptomatic hypotension does not require intervention.
- May improve with time.
- Consider giving dose at night.
- Consider reducing the dose of other hypotensive drugs (particularly vasodilators).
- If symptoms persist, reduce (or as a last resort stop) the ACE-I dose and monitor the patient.

Cough

- Consider alternative causes, i.e. deteriorating HF with pulmonary oedema, lung disease.
- If troublesome, switch to an ARB.

Angioedema

- Discontinue.
- Consider trial of an ARB, although angioedema has also been reported with some ARBs.

Advice to patients

- Explain expected benefits.
- Treatment is given to improve symptoms, to prevent worsening of HF, and to increase survival.
- Symptoms improve within a few weeks to a few months.
- Advise patients to report principal adverse effects, i.e. dizziness/symptomatic hypotension, cough.

Angiotensin II receptor antagonists for heart failure

- Angiotensin II receptor blockers should be used in patients with heart failure or asymptomatic left ventricular systolic dysfunction (LVEF \leq 40%) when an ACE-I is not tolerated (cough).
- As with ACE-Is, ARBs reduce mortality and morbidity (improve symptoms, exercise tolerance, and quality of life, and reduce the need for hospitalization) and improve or at least prevent further deterioration of ventricular function.
- Initial studies (Val-HeFT (Valsartan Heart Failure Trial)), CHARM-Added (Candesartan in Heart Failure—Assessment of Mortality and Morbidity)) suggested an added benefit in mortality and risk of hospitalization for deteriorating HF with the combination of ACE-I and ARB compared to either agent alone. A recent study (ONTARGET (Ongoing Telmisartan Alone and in combination with Rampril) however, demonstrated worse major renal outcomes (composite of dialysis, doubling of serum creatinine, and death) with a combination of ramipril and telmisartan compared to either treatment alone, raising concerns.
- Currently the addition of an ARB on top of optimal ACE-I treatment should be considered in HF patients who remain symptomatic despite optimal doses of ACE-I and β -blocker, when aldosterone antagonists are either not tolerated or contraindicated.
- Contraindications: as with ACE-Is, with the exception of angioedema.
- Initiation as with ACE-Is.
- Practical considerations as with ACE-Is, with the exception of cough.

Doses of angiotensin II receptor blockers used in heart failure

See Table 7.8

Table 7.8 Doses of ARBs used in heart failure

Licensed ARB	Initiating dose (mg)	Target dose (mg)
Candesartan	4 once daily	32 once daily
Losartan	12.5 once daily	100 once daily
Valsartan	40 twice daily	160 twice daily

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Beta-blockers for heart failure

- Unless contraindicated or not tolerated, all patients with symptomatic heart failure or asymptomatic left ventricular dysfunction ($LVEF \leq 40\%$) should receive a β -blocker.
- β -blockers reduce mortality and morbidity (improve symptoms, exercise tolerance, and quality of life, and reduce the need for hospitalization) and improve or at least prevent further deterioration of ventricular function.
- Where possible, β -blockers should be cautiously initiated prior to hospital discharge. Close monitoring is required as there may be an initial deterioration in HF symptoms.

Contraindications

- Asthma is not an absolute contraindication given that β -blockers licensed for use in heart failure are highly cardioselective. We would recommend however, that they are initiated under a specialist's supervision after a trial with short-acting metoprolol while monitoring peak expiratory flow rate (PEFR) and oxygen saturation in a clinical setting with resuscitation facilities.
- Not recommended in patients with severe asthma and regular exacerbations.
- In contrast to popular belief, chronic obstructive pulmonary disease (COPD) is not a contraindication to the use of β -blockers in HF patients. Lung function tests with assessment for reversible airways obstruction using β -agonists (salbutamol) or antimuscarinics (ipratropium) may prove a useful adjunct. If significant reversibility exists, re-evaluate the COPD diagnosis and perform a trial with a short-acting β -blocker.
- Second- or third-degree heart block, sick sinus syndrome (in the absence of a permanent pacemaker).
- Sinus bradycardia (<50 bpm).

Initiation of a β -blocker

- The common practice of adding a β -blocker to a regime containing an ACE-I is based on the fact that the ACE-I trials were performed first, with the β -blocker trials done with the drugs used on top of the ACE-I. Two large trials however (CARMEN (Randomized Controlled Multicentre Trial), CIBIS III (Cardiac Insufficiency Bisoprolol Study)), indicate that the two approaches, i.e. β -blocker first vs. ACE-I first, are comparable, thereby allowing clinicians to select the best approach for their patients with chronic HF. More importantly, the results of these studies support a therapeutic strategy in which the institution of an early combination therapy should not be delayed.
- HF symptoms should be relatively stable prior to initiation.
- Start with a low dose and up-titrate every 2–4 weeks.
- Monitor the patient for symptoms and signs of deteriorating HF, hypotension, or excessive bradycardia.
- Aim for the evidence-based target dose or the maximum tolerated dose.

Practical considerations in treatment of heart failure with β -blockers

Deteriorating symptoms and/or signs of HF

- Exclude co-existent pathology, i.e. increasing breathlessness secondary to bronchospasm in asthma.
- Remember that fatigue can be a direct side-effect of the β -blocker not related to the HF status.
- Increase the dose of diuretics (usually required temporarily).
- If symptoms persist, consider reducing (or as a last resort stopping) the β -blocker dose and monitor the patient.

Symptomatic hypotension

- Asymptomatic hypotension does not require intervention.
- May improve with time.
- Consider reducing the dose of other hypotensive drugs (particularly vasodilators).
- If symptoms persist consider reducing (or as a last resort stopping) the β -blocker dose and monitor the patient.

Excessive bradycardia

- Perform an ECG and/or ambulatory monitoring when necessary to exclude significant heart block, pauses.
- If heart rate is <50 bpm and the patient is symptomatic, discontinue other contributing drugs (digoxin, amiodarone).
- If symptoms persist, consider reducing (or as a last resort stopping) the β -blocker dose, and monitor the patient.

Sexual dysfunction

- May be precipitated or exacerbated by β -blockers.
- Consider reducing the β -blocker dose.
- Refer to a specialist.

Doses of β -blockers used in heart failure

See Table 7.9.

Table 7.9 Doses of β -blockers used in heart failure

Licensed β -blocker	Initiating dose (mg)	Target dose (mg)
Bisoprolol	1.25 once daily	10 once daily
Carvedilol	3.125 twice daily	25–50 twice daily
Metoprolol succinate ^a	12.5 once daily	200 once daily
Nebivolol	1.25 once daily	10 once daily

^aNot available in the UK.

Advice to patients

- Explain the expected benefits.
- Emphasize that treatment is given as much to prevent worsening of HF as to improve symptoms; beta-blockers also increase survival.
- If symptomatic improvement occurs, this may develop slowly—over 3–6 months or longer.
- Temporary symptomatic deterioration may occur (estimated 20–30% of cases) during initiation/up-titration phase.
- Advise the patient to report deterioration and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by adjustment of their medication; patients should be advised not to stop β -blocker therapy without consulting their physician.
- Patients should be encouraged to weigh themselves daily (after walking, before dressing, after voiding, before eating) and to consult their doctor if they have persistent weight gain.

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Aldosterone receptor antagonists in heart failure

- Aldosterone antagonists are indicated in patients with left ventricular dysfunction (LVEF \leq 35%) and severe symptomatic heart failure (NYHA class III or IV), despite treatment with optimal doses of ACE-I and β -blocker.
- Aldosterone inhibitors reduce both mortality and the number of hospital admissions secondary to deteriorating HF symptoms.
- The first-line aldosterone antagonist used in clinical practice is spironolactone (RALES (Randomized Aldactone Evaluation Study)). Eplerenone is indicated in a specific subgroup of post acute MI patients with LVEF \leq 40% and HF or diabetes (EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)) or in those developing endocrine side-effects on spironolactone (10% of males may develop breast tenderness or enlargement).

Contraindications

- Serum potassium >5.0 mmol/L
- Serum creatinine >220 μ mol/L
- Addition to a combination of ACE-I and ARB.

Initiation of aldosterone antagonists

- Check renal function and serum electrolytes.
- Recheck renal function and serum electrolytes 1 and 4 weeks after starting treatment.
- Consider dose up-titration after 4–8 weeks. Do not increase the dose if there is worsening renal function or hyperkalaemia. Recheck renal function and serum electrolytes 1 and 4 weeks after increasing the dose.
- Aim for the evidence-based target dose or maximum tolerated dose.
- Recheck renal function and serum electrolytes 1, 2, 3, and 6 months after achieving the maintenance dose, and 6 monthly thereafter.

Doses of aldosterone receptor antagonists used in heart failure

See Table 7.10.

Table 7.10 Doses of aldosterone receptor antagonists used in heart failure

Licensed aldosterone antagonist	Initiating dose (mg)	Target dose (mg)
Spironolactone	25 once daily	50 once daily
Eplerenone	25 once daily	50 once daily

Practical considerations in treatment of heart failure with aldosterone receptor antagonists

Deteriorating renal function

- Check for other nephrotoxic drugs (NSAIDs).
- If creatinine rises to $>210 \mu\text{mol/L}$, halve the dose of aldosterone antagonist and monitor biochemistry closely.
- If creatinine rises to $\geq 310 \mu\text{mol/L}$, stop the aldosterone antagonist and monitor biochemistry closely.

Hyperkalaemia

- Check for other drugs causing hyperkalaemia (potassium-sparing diuretics, supplements).
- If potassium rises to $>5.5 \text{ mmol/L}$, halve the dose of aldosterone antagonist and monitor biochemistry.
- If potassium rises to $>6.0 \text{ mmol/L}$, stop the aldosterone antagonist and monitor biochemistry.
- Specific treatment of hyperkalaemia may be needed.

Symptomatic hypotension

- Asymptomatic hypotension does not require intervention.
- It may improve with time.
- Consider reducing the dose of other hypotensive drugs (particularly vasodilators).
- If symptoms persist, reduce the dose or stop the aldosterone antagonist and monitor the patient.

Breast tenderness or enlargement

- Switch from spironolactone to eplerenone.

Advice to patients

- Explain the expected benefits.
- Treatment is given to improve symptoms, prevent worsening of HF, and increase survival.
- Symptom improvement occurs within a few weeks to a few months of starting treatment.
- Avoid NSAIDs not prescribed by a physician (self-purchased 'over-the-counter' treatment, e.g. ibuprofen).
- Temporarily stop spironolactone if the patient has diarrhoea and/or vomiting, and contact the physician.

Cardiac glycosides (digoxin) in heart failure

- Digoxin is a useful aid to β -blockers for rate control of AF (when >80 bpm at rest or >110 – 120 bpm at exercise) in patients with HF, but its role is less well established in patients with sinus rhythm or rate-controlled AF.
- Two large digoxin-withdrawal trials (RADIANCE (Randomized Assessment of Digoxin on Inhibitors of ACE) and PROVED (Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin)) demonstrated that patients from whom digoxin was withdrawn were more likely to be admitted with worsening HF.
- The DIG (Digitalis Investigation Group) trial enrolled 6800 patients with classes I to III HF with a mean EF of 28%. This showed that there was no increase in mortality in the group given digoxin. There was a trend to a decrease in mortality due to pump failure, balanced by a slight increase in non-pump-failure-related cardiac deaths. Digoxin reduced the number of hospitalizations for HF significantly.
- Overall, the clinical trials support the use of digoxin in patients in sinus rhythm with mild to moderate HF. Trough levels should be maintained between 0.5 and 1.0 ng/mL.
- Digoxin has been shown to reduce morbidity, i.e. the number of hospitalizations, but not mortality in patients in sinus rhythm (DIG trial; performed prior to the use of β -blockers).
- Digoxin could be used prior to the initiation of a β -blocker in patients with decompensated HF and should be considered where β -blockers are contraindicated.
- Digoxin should be considered in patients in sinus tachycardia, in addition to a β -blocker to control the heart rate (when >80 bpm at rest or >110 – 120 bpm at exercise).
- Digoxin should be considered in symptomatic patients on optimal medical treatment, i.e. on ACE-I, β -blocker and aldosterone antagonist, irrespective of the need for heart-rate control.

Contraindications

- Significant bradycardia (<50 bpm) or 2nd- or 3rd-degree heart block without a permanent pacemaker
- Pre-excitation syndromes (Wolff–Parkinson–White).

Initiation of digoxin

- Unless there is a clinical emergency, oral treatment should suffice.
- The therapeutic serum concentration should be maintained between 0.5 and 1.0 ng/mL.
- Certain drugs (amiodarone, diltiazem, verapamil, certain antibiotics) and renal impairment may increase plasma levels.
- Monitor potassium serum levels (hypokalaemia) and for signs of toxicity.

Hydralazine and isosorbide dinitrate in heart failure

- In chronic HF, the combination of hydralazine and isosorbide dinitrate should be considered:
 - as an alternative to an ACE-I or ARB in patients who do not tolerate either of these drugs
 - as an addition to patients on optimal medical therapy, i.e. ACE-I/ARB, β -blocker, aldosterone antagonist, who remain symptomatic.
- Evidence regarding the use of hydralazine and isosorbide dinitrate is strongest in patients of African descent with the A-HeFT (African-American Heart Failure Trial), demonstrating reduced morbidity (relative risk ratio (RRR): 33%) and mortality (RRR: 43%) in African-American patients in NYHA III or IV.
- Isosorbide dinitrate is the only nitrate formulation that has been shown to increase exercise tolerance, and, in combination with hydralazine, prolongs survival in patients with HF.
- The addition of hydralazine appears to attenuate nitrate tolerance.

Contraindications

- Symptomatic hypotension
- Lupus syndrome
- Severe renal impairment.

Initiation of hydralazine and isosorbide dinitrate

- Starting dose:
 - hydralazine 25 mg three times daily
 - isosorbide dinitrate 20 mg three times daily
- Target dose:
 - hydralazine 75 mg three times daily
 - isosorbide dinitrate 40 mg three times daily
- Monitor for drug-induced lupus (arthralgia, myalgia, rash, unexplained pyrexia, pericarditis, pleurisy, increased antinuclear antibodies (ANA) titre).

Vasodilators in acute heart failure

- Vasodilators are useful in controlling HF symptoms in acute decompensation in patients without symptomatic hypotension.
- Vasodilators should be avoided in patients with systolic blood pressure (BP) < 90 mmHg, as they may reduce central organ perfusion.
- Intravenous nitrates (isosorbide mononitrate, isosorbide dinitrate), sodium nitroprusside, and nesiritide (not available in the UK) can all be used as infusions in the acute setting.
- Calcium antagonists are not recommended in the management of acute HF.

Other pharmacological treatments used in heart failure

Positive inotropic support

- Inotropic agents should be considered in the acute setting in patients with low-output states and signs of hypoperfusion or congestion despite vasodilator and diuretic treatment.
- They should be used with caution in patients with tachycardia (>100 bpm) as they may exacerbate it or precipitate arrhythmias.
- Stimulation of β -receptors may lead to vasoconstriction and elevated systemic vascular resistance.

Dobutamine

- Acts through stimulation of β_1 -receptors to produce a dose-dependent positive inotropic response.
- The elimination of the drug is rapid after the cessation of infusion.
- Care should be exercised when weaning patients off dobutamine infusion, with gradual tapering and simultaneous optimization of the oral treatment.

Dopamine

- Acts through stimulation of β -receptors to produce a positive inotropic response.
- At low doses ($\leq 2-3$ mcg/kg/min), dopamine stimulates dopaminergic receptors and may enhance the diuretic effect. Current trials have not provided any evidence of significant morbidity or mortality benefit with low-dose dopamine in normotensive patients.

Noradrenaline (norepinephrine)

- Not recommended as a first-line inotrope due to its vasopressor effect.
- Only indicated in cardiogenic shock when the combination of a fluid challenge and alternative inotropic agents fails to restore adequate organ perfusion (systolic BP < 90 mmHg) despite an improvement in cardiac output.
- It may also be used in septic patients with HF.
- Exert extreme caution when used in combination with other inotropes, and in particular dopamine which already exerts a significant vasopressor effect at high doses.

Adrenaline (epinephrine)

- Its use should be restricted to cardiac arrest only.

Levosimendan

- Is a unique inotropic agent with dual action: (1) a calcium sensitizer by binding in troponin-C in cardiac myocytes, resulting in improved cardiac contractility and cardiac output; and (2) opening of the ATP-sensitive potassium channels in the vascular smooth muscle, resulting in reduction in systemic and pulmonary vascular resistance.
- It is administered as an IV bolus followed by a 24-hour infusion, and the haemodynamic response may be maintained over several days.

- Current evidence from placebo-controlled trials suggest a favourable effect on symptoms (REVIVE (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy)) and short-term survival (CASINO (Calcium Sensitizer or Inotropic Agent or None in Low Output Heart Failure)) in patients with acute, decompensated heart failure.
- Levosimendan treatment is associated with an increase in heart rate and reduction in blood pressure and should therefore be used with caution in patients with hypotension.
- Clinical trials with oral preparations are ongoing.

Phosphodiesterase inhibitors

- Type III phosphodiesterase inhibitors inhibit the breakdown of cyclic adenosine monophosphate (AMP) and have inotropic and peripheral vasodilating effects, resulting in:
 - increased cardiac output
 - reduced systemic and pulmonary vascular resistance
- Their effects are maintained during concomitant β -blocker therapy.
- They are usually administered as an IV bolus followed by infusion.
- Caution should be exerted in patients with coronary artery disease, as they may increase medium-term mortality (OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure)).

Antiplatelet agents and anticoagulants

- Antiplatelet agents are indicated in patients with HF of ischaemic aetiology (see [📖](#) Chapter 4).
- There is no evidence to support the use of antiplatelet agents in HF of non-ischaemic aetiology. On the contrary, NSAIDs like aspirin should be avoided due to their fluid-retaining and renotoxic effects.
- Oral anticoagulants (warfarin) are recommended in patients with HF and:
 - atrial fibrillation
 - intracardiac thrombus
 - left ventricular aneurysm
 - prosthetic valves
 - other non-cardiac conditions (pulmonary embolism, recurrent deep vein thromboses (DVTs)).
- There is no evidence supporting the use of oral anticoagulation based on a poor EF alone.

HMG-CoA reductase inhibitors (statins)

- Statins are indicated in HF of ischaemic aetiology (CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)).
- There is no indication for statins outside the context of ischaemia or primary cardiovascular prevention.

Device therapy for heart failure

Implantable cardiac defibrillator (ICD)

Secondary prevention

- Survivors of sudden cardiac death secondary to either ventricular tachycardia or ventricular fibrillation
- Spontaneous sustained ventricular tachycardia causing syncope or significant haemodynamic compromise
- Sustained ventricular tachycardia (VT) without significant haemodynamic compromise in patients with a LVEF \leq 35%, who are no worse than NYHA functional class III and have a reasonable expectation of survival for >1 year.

Primary prevention

- Current data suggest that the aetiology of HF may not justify a different approach for primary prevention of sudden cardiac death.
- Data for patients in NYHA I are less robust.
- Post-MI and all of the following:
 - at least 40 days post-MI
 - on optimal medical therapy
 - LVEF \leq 35%
 - NYHA functional class II or III
 - reasonable expectation of survival for >1 year.

(According to the National Institute for Health and Clinical Excellence (NICE) guidelines 2003, documented non-sustained VT on Holter monitor or inducible VT on electrophysiological studies was also a prerequisite.)

- Non-ischæmic cardiomyopathy and all of the following:
 - on optimal medical therapy
 - LVEF \leq 35%
 - NYHA functional class II or III
 - reasonable expectation of survival for >1 year.

Pacemakers

- The conventional indications for the implantation of a permanent pacemaker apply to HF patients.
- Wherever possible, dual-chamber pacemakers should be implanted to maintain atrioventricular synchrony.
- In HF patients with significant symptoms (NYHA II–IV), dilated LV, or severely impaired LVEF (\leq 35%), right ventricular pacing may cause or increase interventricular dys-synchrony and exacerbate symptoms. Cardiac resynchronization therapy (CRT) with pacemaker function should therefore be considered.

Cardiac resynchronization


- Involves the implantation of a biventricular pacemaker, pacing the right and the left ventricles simultaneously.
- Implantation can be challenging and should be performed by experienced operators.
- CRT improves quality of life and functional status (MIRACLE (Multicenter InSync Randomized Clinical Evaluation)), reduces

HF-related hospitalizations (COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Therapy)), and prolongs survival (CARE-HF (Cardiac Resynchronization in Heart Failure)).

- Candidates for resynchronization therapy should satisfy all of the following criteria:
 - optimal medical treatment (or best treatment tolerated)
 - NYHA functional class III–IV
 - LVEF \leq 35%
 - QRS duration \geq 120 ms.
- Although biventricular pacemakers have been implanted in patients without ECG evidence of significant electrical dyssynchrony (QRS $<$ 120 ms) based on echocardiographic evidence of dys-synchrony, there are no studies supporting such a practice. On the contrary, the PROSPECT (Predictors of Response to CRT) trial did not identify any echocardiographic measures of dys-synchrony that reliably predicted patients likely to respond to CRT.
- Resynchronization therapy may be combined with a defibrillator but the benefit of CRT–defibrillator versus CRT–pacemaker only has not been adequately addressed.

Surgery for heart failure

Valve surgery

- Patients with primary valve disease should be considered for valve repair/replacement surgery (see  Valvular heart disease, Chapter 3, p. 143).
- Selected patients with severe functional MR and depressed LV function, who remain symptomatic despite optimal medical therapy may be considered for surgery.
- Surgery for isolated functional tricuspid regurgitation is not recommended.

Coronary artery bypass grafting (CABG)

- CABG and percutaneous coronary intervention (PCI) should be considered in selected patients with HF, after careful consideration of symptoms, objective evidence of myocardial ischaemia (stress-induced ischaemia or hibernating myocardium), co-morbidities, procedural risk, and coronary anatomy.
- Single-centre, observational studies suggest that revascularization may improve symptoms and cardiac function. Clinical trials are ongoing.

Transplantation

Cardiac transplantation is reserved for those patients with end-stage HF. It is a major undertaking for the patient, who must be willing to undergo intensive treatment and be emotionally capable of withstanding the uncertainties that occur both before and after transplantation. There are a number of contraindications, some of which are shown below.

Contraindications for heart transplantation

- Persistent alcohol/drug abuse
- Treated cancer with remission and <5 years' follow-up
- Systemic disease with multi-organ involvement
- Infection
- Fixed high pulmonary vascular resistance.

Despite problems with rejection and complications of immunosuppressive therapy (infection, hypertension, renal failure, malignancy), the 5-year survival is of the order of 70–80%, with many patients returning to work.

Assist devices

Because of the lack of organ donors for cardiac transplantation, much interest has been shown in the development of LV assist devices (LVADs) and mechanical hearts. LVADs are automatic pumps that take over the work of the heart. They have been used as a bridge to transplantation and also as a bridge to recovery in those with potentially reversible causes for their HF (e.g. post-viral).

The next stage up from these large devices is the implantation of a permanent artificial heart. An example is the Jarvik 2000[®], which has been successfully implanted in a relatively small number of patients.

Heart transplantation guidelines adapted from European Society of Cardiology (ESC)/AHA guidelines

Indications	Contraindications and cautions
<ul style="list-style-type: none"> ● Patients must be willing and able to withstand the physical and emotional demands of the procedure and its postoperative sequelae ● Objective evidence of limitation, e.g. peak oxygen consumption less than 10 mL/min/kg on cardiopulmonary exercise test with evidence for anaerobic metabolism^a ● Patients who are dependent on IV inotropes and mechanical circulatory support 	<ul style="list-style-type: none"> ● Current alcohol and/or drug abuse ● Chronic mental illness, that cannot be adequately controlled ● Treated cancer with remission and <5 years' follow-up. ● Systemic disease with multi-organ involvement ● Uncontrolled infection ● Severe renal failure (creatinine clearance <50 mL/min) or creatinine >200 µmol/L, although some centres accept patients on haemodialysis ● Fixed high pulmonary vascular resistance (6–8 Wood units and mean transpulmonary gradient >15 mmHg and pulmonary artery systolic pressure >60 mmHg) ● Recent thromboembolic complication ● Unhealed peptic ulcer ● Evidence of significant liver impairment ● Other disease with a poor prognosis

^aPatients with significant exercise limitation that have a peak oxygen consumption less than 55% predicted or between 11 and 15 mL/min/kg also warrant consideration for cardiac transplantation if they have recurrent unstable myocardial ischaemia that is untreatable by other means, or recurrent episodes of congestive heart failure in spite of adherence to optimum medical therapy.

Heart failure with normal ejection fraction (HFNEF)/diastolic heart failure (DHF)

- The terms diastolic heart failure, heart failure with normal ejection fraction, and heart failure with preserved ejection fraction are used interchangeably.
- Approximately 50% of the HF population have a normal or near-normal LVEF.
- Diastolic dysfunction, however, is not unique to patients with diastolic HF, and often co-exists with systolic dysfunction.
- Compared with patients with heart failure with reduced ejection fraction (HFREF; systolic heart failure), individuals with HFNEF are typically older and more likely to be female.

Pathophysiology

- Impaired active ventricular relaxation
- Impaired passive ventricular filling due to increased ventricular stiffness. The increased stiffness leads to an increase of the LV end-diastolic pressure and pulmonary venous pressure, which in turn leads to increased dyspnoea during exercise and even pulmonary oedema
- Exercise intolerance is thought to be due to a combination of impaired LV filling and inability to utilize the Frank–Starling mechanism, resulting in failure to increase the cardiac output sufficiently during exertion (see Fig. 7.5)
- In contrast to patients with HFREF, who typically exhibit LV dilatation and eccentric LV hypertrophy, patients with HFNEF are characterized by non-dilated LV and concentric hypertrophy (Fig. 7.5)
- Causes of HFNEF are similar to those of HFREF, with ischaemia and hypertension being top of the list. HFNEF is, however, associated with a higher prevalence of hypertension (up to 88%), obesity (up to 40%), renal failure, anaemia, and AF.

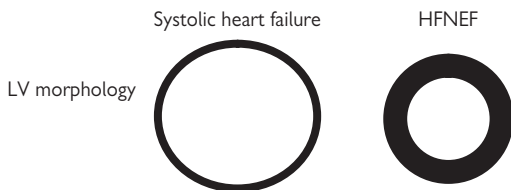


Fig. 7.5 Comparison of the characteristics of LV morphology and function in patients with HF and reduced LVEF and HFNEF. Reproduced with permission from Maeder MT et al (2009). *J Am Coll Cardiol* 53: 905–18.

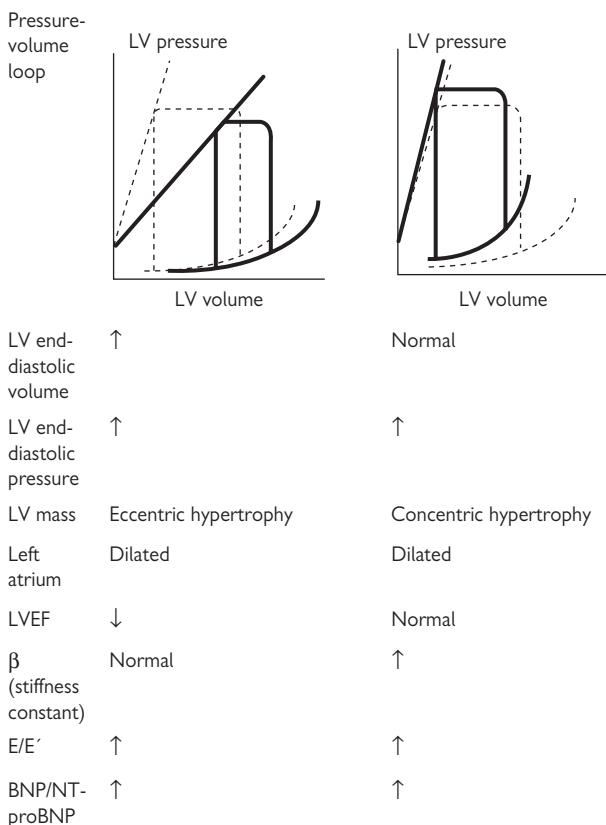


Fig. 7.6 The pressure–volume loops highlight that in patients with systolic heart failure, the slope of the end-systolic pressure–volume relationship, which is obtained by recording pressure–volume loops at different pre-load levels, is typically less steep (solid lines) than in individuals with normal hearts (dashed lines), and the loops are shifted toward larger volumes. In contrast, the end-systolic pressure–volume relationship is steeper or normal in HFNEF. However, HFNEF patients typically exhibit an end-diastolic pressure–volume relationship that is shifted upwards and to the left. LV = left ventricular; E/E' = transmitral peak velocity during early relaxation to early diastolic peak mitral annulus velocity; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Diagnosis and treatment of HFNEF

A diagnosis of HFNEF requires (Fig. 7.7):

- signs and/or symptoms of HF (clinical symptoms and signs of HFNEF are similar to those of HFREF).
- normal or mildly reduced LV systolic function (LVEF > 50%).
- evidence of diastolic dysfunction (although evidence of diastolic dysfunction can be obtained with invasive measurements, transthoracic echocardiography is the investigation of choice in everyday clinical practice).
- every effort should be made to exclude other possible diagnoses that may present in a similar manner, as well as to exclude technical pitfalls on echocardiography (see Fig. 7.8).

Treatment of HFNEF

- Unlike HFREF, there is limited evidence-based treatment for HFNEF.
- LV hypertrophy seems to be an important target for prevention of HF.
- Aggressive treatment of hypertension and diabetes is recommended.
- Diuretics are used for relief of fluid overload and symptom control.
- Given the high prevalence of LVH and diabetes, there is a compelling argument for use of ACE-Is or ARBs. However, none of the randomized controlled trials (CHARM-Preserved (Effects of Candesartan in Patients with Chronic Heart Failure and Preserved LVEF), I-Preserved (Irbesartan in Heart Failure with Preserved Ejection Fraction), PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) using candesartan, irbesartan, and perindopril respectively) to date have demonstrated any convincing mortality benefit.
- As with ACE-Is/ARBs, β -blockers are commonly used in HFNEF. However, once again, there are very limited data to support their use outside the context of hypertension or rate control.
- Restoration of sinus rhythm in patients with AF, and coronary revascularization in patients with significant reversible ischaemia are recommended.

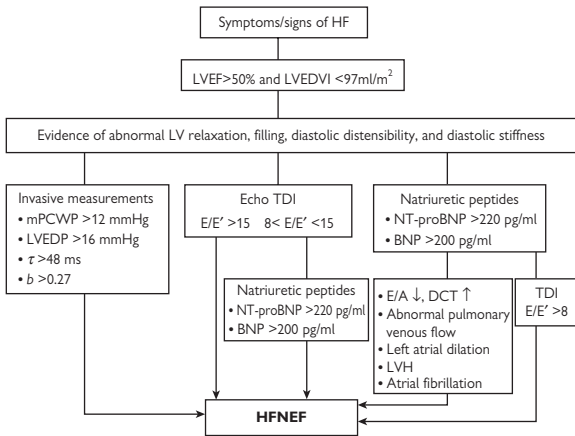


Fig. 7.7 Principles of the algorithm proposed for the diagnosis of HFNEF by the Working Group of the European Society of Cardiology. b = left ventricular passive stiffness; DCT = deceleration time; E/A = ratio of early to late diastolic peak mitral inflow velocities; LVEDVI = left ventricular end-diastolic volume index; LVH = left ventricular hypertrophy; mPCWP = mean pulmonary capillary wedge pressure; τ = time constant of the isovolemic pressure decline; TDI = tissue Doppler imaging. Reproduced from Principles of the Algorithm Proposed for the Diagnosis of HFNEF by the Working Group of the European Society of Cardiology. Paulus WJ *et al. Eur Heart J* 2007;**28**:2539–2550.

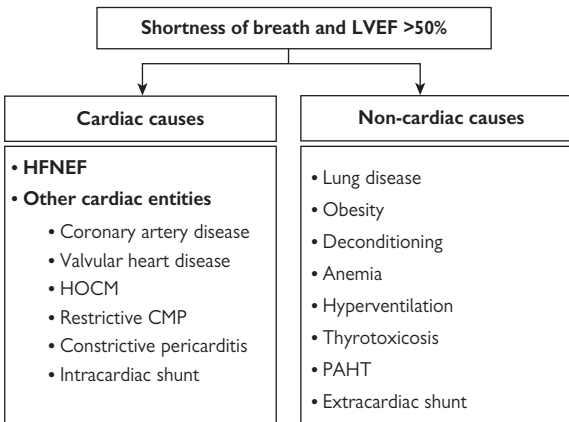


Fig. 7.8 Scheme illustrating the differential diagnoses to the syndrome of HFNEF. HOCM = hypertrophic obstructive cardiomyopathy. Reproduced with permission from Maeder MT *et al* (2009). *J Am Coll Cardiol* **53**: 905–18.

Common co-morbidities in patients with heart failure

Hypertension

- Should be treated aggressively in all HF patients
- Target BP should be <140/90 mmHg and <130/80 mmHg in high-risk groups (proteinuria, renal dysfunction, myocardial ischaemia).

Diabetes mellitus

- Tight glycaemic control is recommended.
- Patients should be treated as per established guidelines.
- Thiazolidinediones have been associated with increased fluid overload and symptomatic HF, and are therefore contraindicated in patients in NYHA functional class III–IV and should be used with caution in less symptomatic patients (NYHA I–II).
- Given the close association of HF and renal dysfunction, renal function should be monitored in patients on metformin, which may require discontinuation in acute exacerbations associated with acute or chronic renal failure.

Renal impairment

- Common in HF; prevalence increase with increasing HF severity, age, diabetes mellitus, hypertension
- Strongly linked to poorer prognosis
- Always look for potentially reversible causes.

COPD

- Common in HF (20–30%).
- Associated with increased morbidity and mortality.
- Although it may be difficult, attempt to quantify the relative contribution of each component to the symptoms of the patient, since it may affect optimal management.
- The majority of COPD patients will tolerate β -blockers well.

Anaemia

- Anaemia of chronic disease is common in HF, with reported prevalence varying widely (up to 70%).
- Anaemia confers increased morbidity and mortality.
- Correction of chronic anaemia has not been established as routine treatment in HF, and blood transfusion is not recommended unless the patient is compromised.
- Erythropoietin treatment has been trialled but remains of unproven benefit.

Gout

- Common in HF, given the use of loop diuretics and high prevalence of renal dysfunction.
- Hyperuricaemia is an independent risk factor of poor prognosis in HF.
- Avoid NSAIDs/steroids and treat acute attacks with colchicine.
- Prophylactic treatment with allopurinol is recommended to prevent recurrence.

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Palliative care for heart failure

- Patients with clinical features of advanced HF, who experience refractory symptoms despite optimal treatment, should be referred for a structured palliative care assessment.
- Symptoms and compromised quality of life, however, prevail throughout the course of HF and should therefore be specifically addressed with palliative care measures.
- Palliative care for HF should be integrated into comprehensive HF care to improve decision making and supportive care:
 - communication
 - education
 - psychological and spiritual needs
 - symptom management.

Worsening heart failure

When a patient is seen with worsening heart failure, it is important to try and ascertain the cause. The most frequent reasons for symptom deterioration are shown next.

Causes of worsening heart failure

Non-cardiac

- Non-compliance (lifestyle changes, medication)
- Newly prescribed drugs
- Renal dysfunction
- Infection
- Pulmonary embolus
- Anaemia.

Cardiac

- Atrial fibrillation
- Other tachyarrhythmias
- Bradycardia/heart block
- Worsening valve disease
- Myocardial ischaemia (including infarction).

Table 7.11 Summary of common side-effects of drugs used in heart failure

Drugs	Complications
Diuretics	<i>Common:</i> postural hypotension, gout, urinary urgency <i>Serious:</i> electrolyte imbalance (hypokalaemia, hypomagnesia, hyponatraemia), arrhythmia
ACE-Is	<i>Common:</i> cough, hypotension including postural <i>Serious:</i> worsening renal function, renal infarction in renal artery stenosis, angio-oedema
β -blockers	<i>Common:</i> tiredness, bradycardia, coldness <i>Serious:</i> asthmatic attack, exacerbation of heart failure, heart block
Spirolactone	<i>Common:</i> gynaecomastia, tiredness, rashes <i>Serious:</i> hyperkalaemia, hypotraemia
Digoxin	<i>Common:</i> nausea <i>Serious:</i> life-threatening arrhythmias
Angiotensin-II receptor antagonists	<i>Common:</i> hypotension including postural <i>Serious:</i> worsening renal function, renal infarction in renal artery stenosis
Amiodarone	<i>Common:</i> photosensitivity, nausea, thyroid dysfunction, sleep disturbance, corneal microdeposits <i>Serious:</i> thyrotoxic storm, pro-arrhythmia, pulmonary/hepatic fibrosis
Inotropes	<i>Common:</i> nausea, palpitation <i>Serious:</i> arrhythmia, cardiotoxicity

High-output heart failure

In high-output states, the only way that the oxygen demands of the peripheral tissues can be met is by an increase in cardiac output. If there is underlying heart disease, the heart is unable to augment the cardiac output in the long term, and HF results.

Causes of high-output states

- Anaemia
- Acquired arteriovenous fistula
- Haemangioma
- Hereditary haemorrhagic telangiectasia
- Hepatic haemangioendothelioma
- Pregnancy
- Acromegaly
- Thyrotoxicosis
- Beri-beri heart disease
- Paget's disease of the bone
- Fibrous dysplasia
- Polycythaemia rubra vera
- Carcinoid syndrome
- Multiple myeloma

Anaemia

When the haemoglobin levels fall below 8 gm/dL, the anaemia produces a high cardiac output. However, even when severe, anaemia rarely causes HF or angina in patients with normal hearts. Look for an underlying cardiac problem or valve disease. Try to determine the aetiology for the anaemia. Patient should be on bed rest and transfused with packed red blood cells accompanied with IV diuretics.

Systemic arteriovenous fistulas

The increase in cardiac output depends on the size of the fistula. The Branham sign consists of slowing of the heart rate after manual compression of the fistula. It also raises arterial blood pressure. Surgical repair or excision is the ideal treatment.

Pregnancy (see 📖 Heart disease in pregnancy, Chapter 15, p. 673)

Thyrotoxicosis

Raised levels of thyroxine produce increased heart rate and cardiac contractility, reduction in systemic vascular resistance, and enhanced sympathetic activation. Thyrotoxicosis does not usually precipitate HF unless there is reduced cardiac reserve. Atrial fibrillation occurs in about 10% of patients, exacerbating the HF. Respiratory muscle weakness may contribute to the dyspnoea.

Beri-beri (see 📖 Beri-beri (thiamine deficiency), p. 664)

Paget's disease

There is a linear relationship between the extent of bone involvement and rise in cardiac output. Involvement of about 15% of the skeleton is required before the rise is seen, and patients may tolerate the early stages well for years. Concomitant valvular disease or ichaemic heart disease results in decompensation. Successful treatment of Paget's disease with bisphosphonates may reverse the rise in cardiac output over several months.

Heart muscle diseases

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Classification

Heart muscle diseases include a diverse range of cardiomyopathies and myocardites. Cardiomyopathies have been previously classified as diseases of unknown cause and were therefore distinct from more specific causes of heart muscle disease such as ischaemia, hypertension, and valvular heart disease. However, a better understanding of their aetiology and pathophysiology has led to this distinction becoming obsolete.

Definition

Cardiomyopathies can be defined as a heterogeneous group of diseases of the myocardium, characterized by mechanical and/or electrical dysfunction that typically (though not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic. Cardiomyopathies are either confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability (Fig. 8.1).¹

Cardiomyopathies can be classified according to the predominant organ involvement. Primary cardiomyopathies are those confined to the heart muscle and can be further subdivided into genetic and acquired forms. Secondary cardiomyopathies occur as part of a variety of generalized systemic diseases, often with multi-organ involvement, which also demonstrate myocardial pathology.

Primary cardiomyopathies

Primary cardiomyopathies are predominantly confined to the heart only. They can be further classified into genetic and acquired groups, though overlap exists with certain forms of cardiomyopathy, in particular dilated cardiomyopathy.

Secondary cardiomyopathies

Secondary cardiomyopathies are typically part of generalized multisystem diseases. Cardiac manifestations may be an isolated feature, though multiple organ involvement is more common. Conversely, if no evidence of myocardial disease is found, regular surveillance for cardiac involvement with history, examination and non-invasive investigations is important. Fig. 8.2 lists examples of conditions associated with secondary cardiomyopathy but is not exhaustive.

¹ Maron BJ, Towbin JA, Thiene G, et al (2006). Contemporary definitions and classification of the cardiomyopathies. An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* **113**: 1807–16.

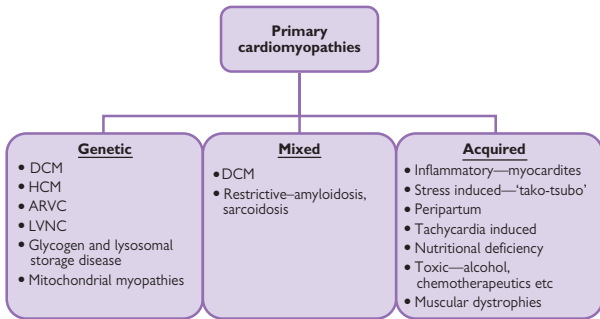


Fig. 8.1 Primary cardiomyopathies can be divided into genetic and acquired causes of heart muscle disease.¹ DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ARVC = arrhythmogenic right ventricular myopathy; LVNC = left ventricular non-compaction.

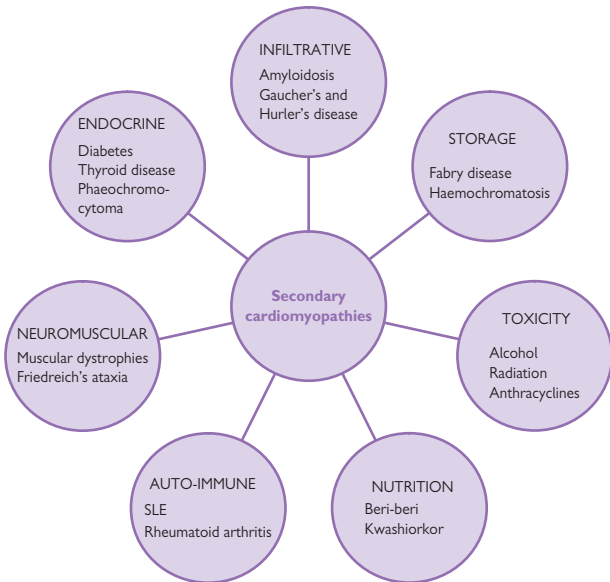


Fig. 8.2 Secondary cardiomyopathies can be a feature of many generalized systemic diseases.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by cardiac chamber enlargement and impaired systolic dysfunction, although diastolic dysfunction is almost always also present. The prevalence is 5–8 per 100 000 and it is 3 times more frequent in black and male than white and female individuals.

Symptoms

Clinical presentation may be abrupt, with acute pulmonary oedema, systemic or pulmonary emboli, or even sudden death, but more often patients present with progressive symptoms of congestive cardiac failure (CCF) including exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and fatigue. Right upper quadrant discomfort, nausea, and anorexia may relate to hepatic congestion. Syncope is an ominous symptom and should be regarded to represent a potentially fatal arrhythmia unless subsequent investigation indicates otherwise.

Diagnosis

Diagnosis is established by physical examination, electrocardiography, chest X-ray (CXR), and echocardiography.

- A raised jugular venous pressure (JVP), displaced cardiac apex, and added heart sounds are sensitive clinical markers of heart failure. Crackles in the lungs and swollen ankles are relatively non-specific, especially in the octogenarian population.
- Electrocardiography (ECG) may show evidence of sinus tachycardia, atrial fibrillation (AF), or frequent ventricular extra-systoles. Voltage criteria for cardiac chamber enlargement, bundle branch block, non-specific T-wave changes, and poor R-wave progression in the anterior chest leads are common.
- CXR may show an enlarged cardiac size and pulmonary oedema (upper lobe venous diversion, interstitial oedema, pleural effusions and Kerley B lines).
- Echocardiography (ECHO) is currently regarded to be the gold standard investigation for diagnosing left ventricular (LV) dysfunction. Bi-atrial and biventricular enlargement are common, and patients with chronic LV volume overload may also exhibit mild left ventricular hypertrophy (LVH). Indices of systolic (and diastolic function) are impaired. The atrioventricular (AV) valves are commonly incompetent, due to annular dilatation. ECHO may reveal complications of dilated cardiomyopathy such as intramural thrombus, and is invaluable in the identification of alternative causes of heart failure, such as hypertensive heart disease, previous myocardial infarction (MI), valvular heart disease, pericardial disease, and intracardiac shunts.
- Exercise testing with or without measurement of maximum ventilatory oxygen consumption, is useful to assess functional capacity and prognosis.
- Ambulatory ECG monitoring is essential to identify the presence of paroxysmal AF and non-sustained ventricular tachycardia (VT), which have important therapeutic and prognostic implications respectively.

- There is rarely any indication for cardiac catheterization in patients with dilated cardiomyopathy, with the exception of excluding coronary artery disease.

Aetiology of dilated cardiomyopathy

Although originally considered to be idiopathic, experimental and clinical data now suggest that genetic, viral, and autoimmune factors play a role in its pathophysiology. Several genetic mutations have been identified as the causative problem in familial DCM, while certain viruses have been shown to cause sporadic cases of DCM. The following list is not exhaustive and there is some overlap with specific cardiomyopathies.


- Inherited (may account for >25% of cases)
- Myocarditis (infective, autoimmune, toxic)
- Metabolic (haemochromatosis, thyrotoxicosis)
- Nutritional (vitamin deficiencies—thiamine (beri-beri))
- Persistent tachycardia (tachycardiomyopathy)

DCM is essentially a diagnosis of exclusion, and potentially reversible causes including coronary artery disease, valvular heart disease, and adult congenital heart disease should be sought. Careful attention should also be paid to dietary history and alcohol consumption, as some reversibility is possible with modification of these factors.


Additional investigations for DCM—the ‘cardiomyopathy screen’

- Renal function
- Liver function tests (LFTs)
- Serum ferritin, iron, transferrin, B₁₂, and folate
- Thyroid function
- Viral serology
- Infective screen (HIV, hepatitis C, enteroviruses)
- Autoantibodies

Dilated cardiomyopathy: treatment

Management of DCM focuses on relieving symptoms and improving prognosis and quality of life. Pulmonary and peripheral congestion are effectively treated with diuretics. Prognostically important pharmaceutical therapies inhibit the maladaptive neurohormonal process involving the sympathetic system and rein-angiotensin-aldosterone axis. The acute management of heart failure is discussed in  Chapter 7, p.367.

Diuretics

Loop diuretics, are useful in relieving symptoms caused by pulmonary and peripheral congestion. Careful monitoring of electrolytes is important, as intravascular depletion may cause urea to rise, and hypokalaemia is common. Hypokalaemia may be counteracted by the co-administration of a potassium-sparing diuretic such as amiloride or spironolactone. Spironolactone is an aldosterone antagonist. The recent RALES (Randomized Aldactone Evaluation Study) trial (see  p. 106) demonstrated that the use of low-dose spironolactone can reduce mortality in patients with severe CCF.

Angiotensin-converting enzyme inhibitors

There is overwhelming scientific evidence that angiotensin-converting enzyme inhibitors (ACE-Is) improve symptoms and outcomes in patients with heart failure, irrespective of symptoms. First-dose hypotension used to be a concern but this is rarely observed with newer ACE-Is and usually only in patients who are relatively intravascularly depleted due to the concomitant use of high-dose diuretics. Side-effects include a dry cough, which may affect up to 20% of patients and is due to increased levels of bradykinin. Angioedema is a rare but potentially life-threatening complication of ACE-Is. Angiotensin receptor 1 antagonists (ARBs) can be used as an alternative in patients who experience a dry cough.

Contra-indications to ACE-I include established bilateral renovascular disease, severe aortic stenosis, pregnancy, and a baseline potassium >6 mmol/L. ACE-Is should be prescribed with caution in individuals with a resting systolic blood pressure <90 mm Hg or baseline creatinine >200 μ mol/L.

Beta-blockers

Beta-blockers also provide symptomatic and prognostic benefit and are recommended in all patients with dilated cardiomyopathy unless there are specific contraindications. Beta-blockers are effective through several mechanisms, which include a reduction of myocardial oxygen consumption, enhanced LV filling, inhibition of the apoptotic effects of catecholamines on cardiac myocytes, treatment of cardiac arrhythmias, and upregulation of beta-1 receptors. Given the potentially negative inotropic effects, the drugs are initiated in low doses, which are titrated up gradually. They should not be started in patients with overt heart failure.

Aldosterone antagonists

Aldosterone antagonists improve symptoms and prognosis and are recommended in patients who continue to remain in NYHA (New York Heart Association) class III despite adequate doses of ACE-I and beta-blockers. The most important complication is hyperkalaemia due to the concomitant use of ACE-I. Painful gynaecomastia is a recognized side-effect, particularly in males taking digoxin and anti-androgens.

Antiarrhythmic agents

Antiarrhythmics agents have not been shown to reduce the incidence of sudden cardiac death (SCD) in patients with DCM. AF is a common arrhythmia in DCM and may be associated with symptoms of cardiac decompensation. Most individuals are rate controlled with β -blockers, although digoxin may be used as additive treatment in individuals who continue to exhibit rapid heart rates despite satisfactory doses of β -blocker. Maintenance of sinus rhythm is usually unsuccessful in the long term.

Anticoagulation

Patients with DCM are prone to thromboembolic complications and should be anticoagulated with warfarin regardless of underlying rhythm.

Device therapy

- Cardiac resynchronization therapy (CRT) utilizes biventricular pacing to combat intraventricular and interventricular dys-synchrony associated with ventricular conduction defects. CRT has been shown to be associated with significant improvements in functional capacity and rates of rehospitalization from heart failure (see p. 404). CRT is generally reserved for individuals with wide QRS complexes (particularly left bundle branch block (LBBB)) who have an ejection fraction (EF) of $<35\%$ and are in NYHA class III despite optimal medical therapy.
- Implantable cardioverter defibrillators (ICDs) are effective in preventing arrhythmogenic SCD and are recommended in all victims of aborted SCD and those with sustained VT. An ICD may be implanted for prophylactic reasons in all individuals with an EF $<35\%$ who are in NYHA class II or III.

Cardiac transplantation

Orthotopic cardiac transplantation using an allograft can be considered in patients who are severely symptomatic despite maximal medical therapy. The limited availability of donor organs still restricts its role. As a result, there is considerable interest in using organs from other species (xenografts). However, technical hurdles still remain before this can be considered a viable option. The artificial heart is another area that has received much interest and publicity, and clinical trials are soon to be conducted.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained LVH and has a prevalence of 1 in 500. HCM is a heterogeneous disorder in terms of clinical manifestation, cardiac morphology, and natural history. Whereas the vast majority of affected individuals have a relatively normal life span, HCM is most recognized for being the commonest cause of exercise-related SCD in young individuals under 35 years of age.

Genetics

HCM exhibits marked allelic and non-allelic heterogeneity, with multiple mutations in at least 12 genes encoding sarcomeric contractile protein. The majority of the mutations (>70%) are in the β -myosin heavy chain, troponin T and myosin-binding protein C genes (see Table 8.1).

Table 8.1 The frequency of sarcomeric gene mutations in HCM

Mutation	Frequency (%)
β -myosin heavy chain	40
Myosin-binding protein C	25
Troponin I	<10
Troponin T	<5
α -Tropomyosin	<5
Myosin light chain	<1
α -Myosin heavy chain	<1
Titin	<0.5
Actin	<0.5

Pathophysiology

The macroscopic hallmark of HCM is LVH, which usually affects the inter-ventricular septum in an asymmetric fashion; however, almost any pattern of LVH is possible, including concentric LVH as seen in individuals with hypertension, and hypertrophy localized to only 1 or 2 myocardial segments. The magnitude of LVH is also variable and can range from very severe LVH (>30 mm) to very mild LVH (13–15 mm). There are also recognized familial cases where the only manifestation of the disorder is an abnormal ECG. Individuals with HCM often exhibit elongated mitral valve leaflets. Histologically, there is evidence of myocyte disarray, myocardial scarring, and abnormal intramyocardial arterioles. Together, these abnormalities manifest as:

- hyperdynamic systolic function, which may be associated with
- left ventricular outflow tract (LVOT) obstruction due to systolic anterior motion (SAM) of the anterior mitral valve leaflet (present in 725% of patients at rest but up to 70% during exercise)

- impaired myocardial relaxation and raised filling pressures
- myocardial ischaemia, and
- propensity to potentially fatal supraventricular tachycardia (SVT) and VT/VF (ventricular fibrillation).

LVOT obstruction occurs as a consequence of forward motion of the anterior mitral leaflet towards the hypertrophied proximal interventricular septum in systole. There are two main postulated mechanisms, which include (1) anterior displacement of the papillary muscles and (2) the so-called Venturi effect, created by rapid ejection of blood across a narrow LVOT, which 'sucks' the anterior mitral valve leaflet against the septum. See also Table 8.2.

Symptoms

Patients with HCM are often asymptomatic and often identified incidentally during routine medical examination, an abnormality on the ECG, or through family screening following the diagnosis in a first-degree relative.

Recognized symptoms may include:

- fatigue and breathlessness due to impaired diastolic filling and decreased cardiac output. Atrial transport is very important for maintaining cardiac output, and symptoms typically deteriorate with AF
- chest pain (angina) may result from increased cardiac work secondary to the LVH, a relative blood supply–demand mismatch, and narrowing of intramural arterioles. High diastolic pressures increase the diastolic wall stress and impair diastolic coronary blood flow
- palpitations, pre-syncope, and syncope may occur due to atrial and ventricular arrhythmias or mechanical obstruction to cardiac output in those patients with left ventricular outflow pressure gradients
- sudden death may be the initial presentation
- approximately 5% of patients may eventually develop progressive left ventricular dilatation and failure, due to ongoing myocardial fibrosis and chronic small-vessel ischaemia.

Physical examination

Look for LVH (a forceful apical impulse and an S₄ heart sound). Outflow tract obstruction is evident by a double apical impulse and ejection systolic murmur beginning in mid-systole, which may be augmented by provocation by manoeuvres such as Valsalva or squatting. A pansystolic murmur due to mitral regurgitation resulting from the SAM of the mitral valve may also be present.

Table 8.2 Dynamic manoeuvres to assess LVOT obstruction

Decreased LVOT obstruction (murmur softer and shorter)	Increased LVOT obstruction (murmur louder and longer)
↑LV volume	↓LV volume
Squatting	Sudden standing
Handgrip	Valsalva (during)
Passive leg elevation	Sublingual glyceryl trinitrate (GTN)
Valsalva (after release)	Hypovolaemia
Mueller manoeuvre (deep inspiration against a closed glottis)	Dehydration
↓Contractility	↑Contractility
Beta-blockers (acute IV)	Beta-agonists (e.g. isoprenaline)
↑Afterload	↓Contractility
Phenylephrine	α-Blockade
Handgrip	

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Hypertrophic cardiomyopathy: investigations

ECG

ECG is abnormal in >95% of cases. Isolated Sokolow–Lyon criterion for LVH is identified in only 2% of cases. Features include:

- ST- and T-wave abnormalities
- LVH with Romhilt–Estes points' score >5
- pathological Q waves in inferior and lateral leads (septal hypertrophy)
- deep T-wave inversions (particularly in anterior and inferior leads in the apical form of HCM)
- pre-excitation and Wolff–Parkinson–White (WPW) syndrome
- ventricular ectopics
- atrial fibrillation.

Echocardiography

Echocardiography continues to remain the gold standard investigation due to its widespread availability. The investigation is usually for detection of the presence, magnitude, and distribution of LVH, as well as identifying patients with basal LVOT obstruction. Recognized echocardiographic features include:

- asymmetric septal hypertrophy (ASH): grossly thickened septum compared with posterior LV wall, with reduced septal motion; however, almost any pattern of LVH is possible
- small LV cavity
- SAM: systolic anterior movement of the mitral valve apparatus
- mid-systolic aortic valve closure or fluttering of the aortic valve leaflet tips
- impaired diastolic function and left atrial enlargement.

Cardiac magnetic resonance imaging (MRI)

Cardiac MRI is extremely helpful for identifying apical HCM, evaluating the anterolateral free wall, and demonstrating evidence of myocardial scarring and fibrosis.

Other investigations

Other investigations may help in risk stratification, although no single investigation accurately predicts those at risk of SCD, and negative tests do not entirely exclude the risk of SCD:

- ambulatory ECG monitoring—AF and ventricular tachycardia arrhythmias. Non-sustained VT is a risk factor for SCD
- exercise testing—functional capacity and blood pressure response to exercise. A flat blood pressure response during exercise (failure of the systolic blood pressure to rise by 25 mmHg from rest to peak exercise, or a paradoxical drop in systolic blood pressure during exercise) is a recognized risk marker for SCD
- there is no role for cardiac catheterization in the diagnosis of HCM, although coronary angiography may be performed in adult patients with angina to exclude co-existent coronary artery disease (CAD)

- there is no role for electrophysiology studies in the diagnosis of HCM. Ventricular stimulation studies have a poor predictive accuracy for the identification of high-risk patients; however, radiofrequency ablation of accessory pathways and atrial flutter circuits may be therapeutically important
- genetic testing is being utilized increasingly; however, a genetic diagnosis is currently only possible in 60–70% of cases. Genetic testing is particularly useful for cascade screening of family members if a causative gene in the proband can be identified.

Hypertrophic cardiomyopathy: treatment

Approximately half of sudden deaths in HCM occur during or shortly after strenuous exercise, and therefore patients should be advised against competitive sports of a high-dynamic and high-intensity nature. The management of HCM includes (1) amelioration of symptoms including abolition of LVOT obstruction; (2) treatment of arrhythmias; (3) identification of individuals at risk of SCD, with a view to implantation of ICD; and (4) screening first-degree relatives for the disorder.

Treatment for symptoms

β-blockers

β-blockers are the mainstay of therapy for angina, dyspnoea, giddiness, and syncope. They reduce myocardial oxygen demand and improve diastolic filling, and are effective in the treatment of angina and exertional dyspnoea. Large doses may be required.

Calcium-channel antagonists

Calcium-channel antagonists (verapamil and diltiazem) are as effective as β-blockers and may be used in patients in whom β-blockers are not tolerated or are contraindicated.

Management of arrhythmias

Beta-blockers and amiodarone are the anti-arrhythmic agents of choice in the management of supraventricular arrhythmias. None of these agents have been shown to reduce the risk of SCD. AV re-entrant tachycardia and atrial flutter are usually amenable to radiofrequency ablation. Sustained VT is treated with amiodarone but such patients are candidates for ICD; the amiodarone reduces the frequency of non-sustained ventricular tachycardia (NSVT) and the need for recurrent anti-tachycardia pacing. Patients with AF should be anticoagulated with warfarin.

Abolition of left ventricular outflow obstruction

Left ventricular outflow obstruction is treated pharmacologically, surgically, or by alcohol-induced transcatheter septal ablation.

- *Drugs*: the drugs of choice include β-blockers or verapamil. Disopyramide, a negatively inotropic agent may be added in those with large symptomatic pressure gradients.
- *Surgical myomectomy*: surgical septal myotomy–myectomy (Morrow procedure) directly debulks the proximal septum. It has been shown to relieve obstruction in 90% of cases and symptoms in 70% over 5 years. The procedure is complicated by a risk of high-degree AV block, requiring permanent pacing, and long-term complications include aortic regurgitation.
- *Transcatheter septal ablation*: alcohol septal ablation involves chemical infarction of the proximal portion of the interventricular septum by injection of alcohol into the first or second septal perforator artery. Initially, results have been promising; however, a significant number of patients (10–25%) are rendered with complete heart block, necessitating permanent pacing. Unfortunately, there remain concerns

about the procedure in terms of the long-term impact of MI, notably adverse LV remodelling of potentially sinister arrhythmias.

- *Cardiac pacing*: dual-chamber pacing with short AV delay has been shown to improve symptoms and abolish gradients in a small proportion of patients. In previous trials, most patients were asymptomatic for only short periods and therefore the procedure is only reserved for patients with severe symptomatic obstruction who are unsuitable for surgery or transcatheter septal ablation.

Sudden cardiac death

The only effective therapy to prevent SCD is an ICD. Definitive (secondary) indications for an ICD include previous aborted SCD or haemodynamically unstable VT.

Risk stratification in patients who are relatively asymptomatic and do not fall into this category is less straightforward. There are currently several established risk factors; however, all have a relatively low sensitivity or specificity to predict SCD in isolation.

The box below lists established risk factors for SCD. Each risk factor has a positive predictive accuracy of 20–25%; however, the negative predictive accuracy of these risk factors exceeds 90%; therefore the absence of any of these risks allows reassurance in most patients. Due to the relatively low positive predictive accuracy of any one of the factors in isolation, current practice indicates that at least two or more of these risk factors should be present to warrant ICD implantation for the purposes of primary prevention.

Markers of risk for SCD in hypertrophic cardiomyopathy

- Markers of risk for SCD in HCM
- Unheralded syncope
- Family history of SCD from HCM
- Severe LVH (>30 mm)
- Severe left ventricular outflow obstruction (>60 mmHg)
- Non-sustained VT on ambulatory ECG monitoring
- Abnormal (flat or decreasing) blood pressure response to exercise.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is a rare condition characterized by impaired diastolic function due to reduced ventricular compliance. It is very important to distinguish restrictive cardiomyopathy from constrictive pericarditis, as the latter can be treated surgically by stripping the pericardium from the myocardium.

Aetiology

The aetiology of truly idiopathic cases remains obscure. A few cases are familial and tend to be associated with skeletal muscle disease. Other cases are associated with systemic diseases, infiltration, or endomyocardial fibrosis.

Symptoms

Patients often have severely limited exercise tolerance due to an inability to increase cardiac output, as their stroke volume is relatively fixed. They are also limited by breathlessness and have evidence of right heart failure (peripheral oedema).

Diagnosis

Physical examination

In addition to signs of CCF, a loud S_3 , S_4 , or both may be present. There also may be prominent x and y descents of the JVP, and venous pressure may increase on inspiration (Kussmaul sign). The apex beat will be palpable, in contrast to constrictive pericarditis.

Investigations

- ECG may show P mitrale or P pulmonale, reduced precordial QRS voltages, and atrial arrhythmias.
- Echocardiography may be normal, or at least demonstrate normal systolic function. Alternatively, systolic function may be reduced in advanced cases. Infiltration may be evident by hypertrophied ventricles, and thickened intra-atrial septum, and the myocardium may appear speckled. Bi-atrial enlargement may also be present. A restrictive mitral inflow pattern is seen on Doppler tracing.
- Laboratory tests are aimed at determining causes of infiltration. Left and right heart catheterization may be necessary to help to exclude constrictive pericarditis (a difference in left (LVEDP) and right (RVEDP) end-diastolic pressures >7 mmHg at end-expiration makes constriction unlikely).
- Computed tomography (CT) and MRI scanning are useful to look at pericardial disease.

Treatment

Treatment is aimed at the symptoms of CCF and the underlying condition. Rate control in AF is important, as reducing ventricular filling times will have significant impact. Patients with amyloid are very sensitive to digoxin.

Causes of restrictive cardiomyopathy

Myocardial

- Non-infiltrative
- Idiopathic
- Scleroderma
- Infiltrative
- Amyloid
- Sarcoid
- Storage diseases
- Lysosomal storage disease (Gaucher's, Hurler's, Fabry)
- Glycogen storage disease
- Haemochromatosis.

Endomyocardial

- Endomyocardial fibrosis
- Hypereosinophilic syndrome
- Metastatic malignancies
- Carcinoid
- Iatrogenic (radiation anthracyclines).

Cardiac amyloidosis

Amyloidosis is a clinical disorder characterized by extracellular deposition of insoluble fibril proteins. Amyloid deposition can occur in connective tissue or blood vessels, and in a variety of organs including the heart, kidney, liver, and nervous system. Cardiac amyloidosis is defined clinically by signs of myocardial or conduction system dysfunction, due to involvement of the heart by amyloid deposition either as part of systemic amyloidosis or as a localized process.

Classification

Systemic AL amyloidosis is the commonest form of clinical amyloid disease. AL fibrils consist of monoclonal immunoglobulin light chains and can be derived from any B-cell dyscrasia (e.g. myeloma, lymphoma), though benign monoclonal gammopathies are commonest. The disorder occurs equally in males and females over the age of 50 years, and usually infiltrates multiple organs. Cardiac involvement occurs in up to 90% of patients with AL amyloidosis, with approximately 50% suffering diastolic heart failure.

Systemic AA amyloidosis is a consequence of any chronic inflammatory condition that features a sustained acute phase response causing elevated production of serum amyloid A protein. Cardiac involvement is rare, but renal disease is the predominant finding, with proteinuria and renal failure.

ATTR cardiac amyloidosis is a form of hereditary systemic amyloidosis with autosomal dominant inheritance due to a mutation in the transthyretin molecule (ATTR). The most common ATTR amyloid cardiomyopathy is due to the Val122Ile mutation (substitution of isoleucine for valine at position 122) and is more prevalent in African-Caribbean individuals, causing late-onset cardiomyopathy and progressive severe heart failure.

Senile systemic amyloidosis is a slowly progressive infiltrative cardiomyopathy. There is a male preponderance, with a prevalence of 25–36% in males aged over 80 years. It is rare in individuals under 60 years, and has a slower progression than AL amyloidosis, despite there being greater cardiac infiltration.

Pathophysiology

Infiltration of the ventricular myocardium with amyloid fibrils is associated with reduced compliance and impaired myocardial relaxation. Left and right atrial pressures become progressively elevated, resulting in pulmonary oedema and peripheral volume overload. Endocardial involvement results in mitral and tricuspid regurgitation, causing a further increase in atrial pressures. Amyloid fibrils within the myocardium promote inflammation and fibrosis, and increase the propensity to fatal re-entrant arrhythmias. Atrial dilatation predisposes to AF. Direct involvement of the cardiac conduction tissue is associated with heart block and sudden death. Deposition of amyloid within coronary arteries is recognized, and may be associated with angina or sudden death. Pericardial involvement is characterized by small effusions, which are usually of little clinical significance.

Clinical features

Isolated cardiac involvement is seen in <4% of individuals with amyloidosis. The clinical presentation is dominated by right-sided heart failure, with left-sided heart failure becoming evident in later stages of the disease. Angina is rare, and due to amyloid deposition in the intramyocardial coronary arteries. Dizziness and syncope are due to several factors, including postural hypotension secondary to autonomic neuropathy, over-diuresis, and tachy- and bradyarrhythmias.

Clinical signs: raised JVP, hepatomegaly, lower-limb oedema, and ascites are common. In advanced cases, LV involvement is associated with hypotension and pulmonary oedema. Precordial examination characteristically reveals a loud third heart sound, due to rapid and abrupt filling of the ventricles in early diastole.

Diagnosis

Cardiac amyloidosis should be suspected in any patient with unexplained heart failure, particularly if there is echocardiographic evidence of LVH with a normal cavity dimension.

ECG: Is non-specific; however, diminished voltages (QRS <0.5 mV in limb leads and <1 mV in precordial leads) and pseudoinfarct patterns with pathological Q waves and T-wave inversion are observed in up to 50% of cases. Atrial fibrillation and flutter are the commonest arrhythmias, followed by varying degrees of heart block.

Echocardiography: Thickening of the LV walls with normal cavity dimensions and diastolic dysfunction are early features. The myocardium exhibits a characteristic 'speckled' appearance. Thickened endocardial surfaces, regurgitation of the AV valves, bi-atrial enlargement, a bright interatrial septum, and small pericardial effusions are also recognized. In advanced stages of the disease process, there is worsening ventricular compliance, resulting in restrictive filling and a marked increase in left and right atrial pressures. Systolic dysfunction is more prevalent in late stages of disease progression.

Cardiac MRI: Is now an established investigation, which shows a characteristic global subendocardial enhancement with late gadolinium enhancement.

Nuclear imaging: Using radio-labelled technetium can detect the distribution of serum amyloid protein but is rarely utilized in practice, due to technical difficulties with hollow and moving organs.

Tissue biopsy: Of the endomyocardium is the gold-standard investigation and is diagnostic when tissue sections are stained with Congo red. Sections demonstrate an 'apple-green' colouration when visualized under polarized light. Tissue diagnosis is rarely necessary in the presence of characteristic myocardial appearances on the echocardiogram and cardiac MRI.

Biochemistry: The cardiac biomarkers troponin I, troponin T and N-terminal pro-B-type natriuretic hormone (NT-proBNP) are elevated in cardiac amyloidosis. Raised troponins are due to amyloid deposition causing myocytes necrosis and small-vessel ischaemia. BNP levels are raised secondary to diastolic dysfunction and often precede the onset of clinical heart failure.

Immunology: Serum immunoelectrophoresis and urinalysis for light chains is essential to exclude an underlying paraproteinaemia.

Cardiac amyloidosis: treatment

Treatment for cardiac amyloidosis is generally supportive, though there are chemotherapeutic and anti-inflammatory treatments aimed at suppressing the expression of serum amyloid A protein and serum immunoglobulins. Symptomatic treatment of heart failure with diuretics and aldosterone antagonists is the mainstay of treatment. There is no evidence that ACE-Is are beneficial in cardiac amyloidosis. Indeed, the venodilatation associated with ACE-Is may potentially reduce ventricular filling and diminish cardiac output. Beta-blockers may also be potentially detrimental in individuals requiring an adequate chronotropic response to maintain cardiac output in the presence of severe impairment of myocardial relaxation.

Digoxin and calcium-channel blockers are contraindicated in cardiac amyloidosis, as they selectively bind to amyloid fibrils causing cardiac toxicity. Anticoagulation must be considered, due to an increased risk of intracardiac thrombus and also due to AF and LV systolic dysfunction.

Cardiac pacing is necessary in patients with heart block. The role of ICDs is contentious when one considers that most patients with symptomatic cardiac amyloidosis survive less than one year. The role of biventricular pacing is not established. Results of cardiac transplantation followed by high-dose chemotherapy or autologous stem cell transplantation are awaited.

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Fabry disease

Fabry disease is a rare X-linked recessive lysosomal storage disorder caused by mutations encoding the enzyme α -galactosidase A. This enzymatic defect leads to accumulation of globotriaosylceramide in several organs including the skin, nervous system, kidney, eyes, and heart. The disorder has a prevalence of 1 in 40 000. Despite the X-linked pattern, women may also exhibit the Fabry disease phenotype, albeit mildly.

Extra-cardiac manifestations

Fabry disease is a multisystem disorder with a progressive clinical course. Clinical manifestations are usually evident by 10 years of age, with cutaneous angiokeratomata (affecting the hips, groins, and umbilical region) and painful neuropathy affecting the hands and feet (acroparaesthesia) being predominant features. Hypohidrosis, heat intolerance, and gastro-intestinal disturbance also occur. In the second decade, proteinuria, corneal opacities, retinopathy, and vestibular and hearing deficits can occur. By the third decade, renal failure, cerebrovascular disease, and cardiomyopathy may be evident, causing significant morbidity and mortality in affected patients.

Cardiac manifestations

Cardiac involvement in Fabry disease may take two forms. There can be multi-organ disease, in which cardiac involvement is a feature, but also an atypical variant in which cardiac manifestations occur in isolation. Hypertension, LVH, conduction defects, coronary artery disease, aortic and mitral incompetence, and aortic root dilatation can all occur. Accordingly, affected individuals may present with angina, dyspnoea, and palpitations.

Investigations

ECG: Findings include LVH most commonly. Short PR interval and conduction disorders of the AV node, His bundle, or its branches can all occur.

Echocardiography: Abnormalities include the presence of LVH, which can be the earliest and only finding. Atrial enlargement, aortic root dilatation, and valvular thickening (aortic and mitral valves) can also be a feature. The increased ventricular wall thickness is due to deposition of globotriaosylceramide within cardiac myocytes. The increased wall thickness may mimic HCM, but thickening is generally symmetric. Systolic and diastolic function are often preserved. Cardiac MRI may be useful in differentiating other forms of cardiomyopathy, particularly when LVH is the predominant echocardiographic feature (distribution of hypertrophy, large papillary muscles and trabeculae, RV hypertrophy, posterior wall gad).

Coronary angiography: Is performed due to a combination of anginal symptoms and an ischaemic-looking ECG. In the majority of cases, coronary angiography is normal, with the ischaemic manifestations due to endothelial dysfunction induced by globotriaosylceramide deposition within coronary arteries.

24-hour Holter monitoring: AF is the commonest arrhythmia, followed by VT. Due to lipid deposition throughout the cardiac conduction tissue, any form of heart block can occur and may require permanent pacemaker implantation.

Endocardial biopsy: The diagnosis may be ascertained by endomyocardial biopsy. Sarcoplasmic vacuolization is the classic finding on light microscopy of haematoxylin and eosin-stained tissue.

Management

There is no definitive cure for Fabry disease, but enzyme-replacement therapy has been demonstrated to cause greater clearance of microvascular endothelial deposits of globotriaosylceramide in the heart and kidneys. It has also been shown to reduce LVH and enhance regional myocardial function. Given this potential for effective therapy, screening for Fabry disease by measurement of plasma α -galactosidase A in patients with unexplained concentric LVH is prudent. Screening should be considered in all first-degree relatives of individuals diagnosed with Fabry disease, and in patients diagnosed with hypertrophic cardiomyopathy, particularly if LVH is symmetrical, and there is no family history of hypertrophic cardiomyopathy.

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary cardiac disorder characterized by fibro-fatty replacement of the right ventricular myocardium, and a predilection to potentially fatal ventricular arrhythmias. The disorder may progress to right ventricular dilatation and failure. In some advanced cases, the left ventricle is also involved, although there is a clinical variant with isolated LV disease. The prevalence is reported as between 1 in 2000 and 1 in 5000.

Aetiology

Between 40% and 50% of cases are familial with an autosomal dominant pattern of inheritance. Several loci have been mapped to chromosomes 1, 2, 3, 10, and 14, causing mutations in genes encoding desmosomal proteins (e.g. plakoglobin, desmoplakin, plakophilin, and desmoglein). An autosomal recessive variant associated with palmoplantar keratosis, wooly hair, and a more malignant clinical course (Naxos disease) has been mapped to the plakoglobin gene on chromosome 17.

Pathophysiology

Macroscopically, the typical structural changes in ARVC include RV dilatation with associated RV myocardial thinning and fibro-fatty infiltration. Particular sites involved include the RV apex, inflow tract, and outflow tract. With disease progression, further involvement of the RV free wall leads to aneurysms and RV cavity dilatation. Left ventricular involvement can be a late feature, and is associated with a higher incidence of arrhythmia and heart failure. Histology demonstrates a segmental transmural fibro-fatty replacement of myocardium with areas of focal myocarditis and inflammatory infiltration. The focal fibro-fatty deposits are the arrhythmogenic substrate that is a hallmark of ARVC.

Symptoms

Patients are often asymptomatic but symptoms of palpitations, pre-syncope and syncope can occur and may be precipitated by exercise. ARVC can present at any age in either sex, and the first presentation in healthy young individuals may be exercise-related SCD. Overt signs of right heart failure are rare. Other patients present in later life with symptoms of CCF with or without ventricular arrhythmias, and advanced cases may be misdiagnosed as having DCM. The natural history of ARVC may be separated into a number of distinct phases with progressive development of symptoms and structural abnormalities:

- *concealed phase*: a subclinical asymptomatic phase with little or no structural RV abnormality. Sudden CD may still occur in this stage of disease
- *overt electrical disorder*: typically with symptomatic ventricular arrhythmias of RV origin. Arrhythmia may vary from premature ventricular beats to non-sustained ventricular tachycardia to ventricular fibrillation. Structurally, there is clear evidence of RV wall involvement

- *RV failure*: progressive loss of RV myocardium due to fibro-fatty replacement impairs RV function and may result in severe pump failure. Gross dilatation of the RV occurs
- *biventricular failure*: an advanced stage with involvement of the interventricular septum and LV causing CCF and imitating DCM.

Diagnosis

Diagnosis of affected individuals can be very difficult, especially during family screening, as standard non-invasive investigations have poor sensitivity. Diagnosis relies on symptoms, a family history of ARVC, ECG abnormalities, and structural changes of the RV on imaging studies. A diagnosis is based on the presence of two 'major'; one 'major', and two 'minor'; or four 'minor' criteria from differing categories.

Investigations

- *12-lead and signal-averaged ECG*: 12-lead ECG may be normal in ~40% of affected individuals. T-wave inversion in the right ventricular precordial leads (V_1 – V_3) is the predominant abnormality. There may also be QRS prolongation with late potentials, known as Epsilon waves, again in leads V_1 – V_3 , suggesting delayed ventricular depolarization. Signal-averaged ECG demonstrates late potentials in 50–80% of individuals with ARVC.
- *Echocardiogram (±cardiac MRI scan)*: echocardiography may be normal, particularly in the 'concealed' phase of ARVC. Findings can vary from mild focal RV hypokinesia to severe RV dilatation with aneurysm formation and reduced function. LV involvement and biventricular failure are late features. Cardiac MRI (CMR) is more sensitive in identifying RV pathology in ARVC, and is now increasingly available. It can assess ventricular volumes, and global and regional ventricular function, as well as myocardial fat and late gadolinium enhancement.
- *24-hour ambulatory ECG monitoring*: frequent ventricular ectopy (>1000/24 hours) and non-sustained or sustained ventricular tachycardia with a LBBB morphology (indicating origin in the RV) are recognized features of ARVC.
- *Exercise testing*: may provoke frequent ventricular ectopy and ventricular tachycardia in patients with ARVC.
- *Invasive procedures*: CMR has superseded RV angiography. Electrophysiological studies are useful in differentiating an RV outflow ectopic focus from ARVC. Electro-anatomical mapping is being utilized to identify scar tissue. Tissue diagnosis is problematic, as a transmural sample is necessary. Furthermore, the disease usually affects the thinnest parts of the RV, increasing the risk of RV perforation. The disease is patchy; therefore, a negative biopsy does not exclude pathology.

ARVC: management

Treatment

There are no established best treatment options for patients with ARVC, and, as the disease is progressive, antiarrhythmic options are used for symptomatic benefit in patients with haemodynamically well-tolerated ventricular arrhythmias. Given the association between exercise and SCD in ARVC, excessive training or participation in sport must be avoided. Patients who have developed RV \pm LV dysfunction can be managed with standard treatments for CCF, and in severe cases transplantation may be an option.

Antiarrhythmics

β -blockers alone or in combination with class I and III antiarrhythmics are the most effective in reducing symptomatic but well-tolerated ventricular arrhythmias. Sotalol and amiodarone have been shown to be most effective.

Radiofrequency ablation

A small subset of patients with drug-refractory arrhythmias who are felt to have fairly localized disease may be amenable to electrophysiologic mapping and radiofrequency ablation. However, it must be remembered that ARVC is a progressive disease, and such procedures cannot be regarded as a permanent cure for future arrhythmias.

Implantable cardioverter defibrillators

In patients with life-threatening or drug-refractory ventricular arrhythmias and widespread disease, ICDs probably offer the best protective measure against SCD.

Risk stratification

There are no established or proven specific risk factors for SCD, but markers of increased risk include young age at presentation, malignant family history, unheralded syncope, right ventricular dysfunction, left ventricular involvement, presence of VT on ambulatory monitoring, QRS dispersion of >40 ms, and certain genetic mutations (in particular Naxos disease).

Further reading

The task force criteria for diagnosis of ARVC are available:

Marcus FI, McKenna WJ, Sherrill D, et al (2010). Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation* **121**(13): 1533–41. Also available to download from <http://eurheartj.oxfordjournals.org/content/early/2010/02/16/eurheartj.ehq025.full.pdf>.

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Left ventricular non-compaction

Left ventricular non-compaction (LVNC) is a rare cardiomyopathy characterized by marked trabeculations and deep intertrabecular recesses in the left ventricular wall. The disorder is also characterized by systolic and diastolic dysfunction, predilection to arrhythmias, and systemic thromboembolism. The prevalence of LVNC is unknown and there is still debate over specific diagnostic criteria. The nomenclature of the condition is misleading, as both the right and left ventricle are commonly involved.

Aetiology

Although the mechanism leading to LVNC is unclear, it is believed to be a disorder of retarded endomyocardial morphogenesis. In normal circumstances, trabeculations in the fetal myocardial primordium occur at day 32 of embryonic development, before inverting ('compacting') by day 70. LVNC represents an arrest of this normal compaction process *in utero*, resulting in a layer of non-compacted myocardium lying adjacent to a compacted layer of endocardium.

A genetic basis for LVNC has been demonstrated by a higher prevalence of the condition in first-degree relatives. The inheritance pattern, however, is variable, with autosomal dominant, X-linked and even mitochondrial transmission being identified. Mutations of *G4.5*, which encodes taffazins expressed in heart and skeletal muscle cells, were initially identified in Barth syndrome. Other mutations encoding structural proteins, such as α -dystrobrevin, Cypher/ZASP and FKBP12, have also been associated with LVNC.

Clinical features

The major clinical manifestations of LVNC are of systolic and diastolic dysfunction and congestive cardiac failure. There is a high prevalence of atrial and ventricular arrhythmias, with WPW common amongst children with the condition. Sudden death due to ventricular tachyarrhythmia has been reported. Systemic emboli due to stagnation of blood in the deep intertrabecular recesses can occur as a presentation or a complication of LVNC.

LVNC is occasionally associated with other congenital cardiac conditions, including Ebstein's anomaly, bicuspid aortic valve, and congenital right or left ventricular outflow tract abnormalities such as pulmonary atresia. It is also associated with certain neuromuscular disorders including Charcot-Marie-Tooth disease and Melnick-Needles syndrome.

Diagnosis

Based on relatively limited data from a small number of centres, the 12-lead ECG is abnormal in up to 95% of cases but changes are non-specific. Features include biventricular hypertrophy, T-wave inversions, and conduction abnormalities including complete heart block. The mainstay of investigation for LVNC is through imaging, particularly echocardiography.

Echocardiography

Some controversy surrounds specific diagnostic criteria for LVNC, but there are three separate criteria, which include:

- the presence of multiple trabeculations particularly at the apex and left ventricular free wall
- multiple deep intertrabecular recesses communicating with the left ventricular cavity, demonstrable particularly with colour Doppler imaging
- a two-layered structure to the endomyocardium with a non-compacted to compacted thickness ratio of greater than 2.0 in adults at end-systole in the parasternal short-axis view.

Other findings may include reduced left ventricular systolic function, diastolic dysfunction, left ventricular thrombi, and abnormal papillary muscle structure.

Cardiac magnetic resonance imaging

CMR is of particular use when satisfactory echocardiographic images are unattainable. It has also superseded the use of cardiac computed tomography and left ventriculogram in assessing for LVNC in difficult cases. The best distinguishing feature for LVNC using CMR was a maximum ratio in diastole of non-compacted to compacted myocardial thickness of greater than 2.3 as assessed in three long-axis views.

Genetic analysis

Muscle biopsies, metabolic studies, and genetic testing may be helpful when LVNC is considered as part of a genetic or metabolic syndrome.

Management

There is no specific therapy for LVNC. Medical management varies with the clinical manifestations, and centres on treatment of heart failure using standard medications. Anticoagulation is usually recommended in patients with AF and/or a LVEF of <40%, to prevent systemic thromboembolism. Monitoring with 24-hour Holter analysis should be considered annually to detect asymptomatic arrhythmias. ICD therapy is recommended in patients with LVNC who have significant left ventricular systolic impairment and non-sustained ventricular tachycardia.

Prognosis

Initial studies on small groups of severely affected individuals suggested that LVNC was associated with a significantly poorer prognosis than other forms of cardiomyopathy, with higher rates of mortality and morbidity. However, with increasing awareness of LVNC, more subtle forms in mildly symptomatic patients or severe forms in asymptomatic patients have been detected.

Ischaemic cardiomyopathy

This is a condition defined as significantly impaired left ventricular function ($EF < 35\%$) in which CAD causes a picture that is often indistinguishable from DCM with or without a preceding history of angina or MI. Often the degree of dysfunction is inconsistent with the extent of CAD. There are two main pathological processes, which can be distinguished by the possibility for corrective therapy. Firstly, there is irreversible loss of myocardium from previous MI and subsequent ventricular remodelling. There is no scope for recovery of myocardial function, as the infarcted tissue is no longer viable. Secondly, there are those patients with hibernating viable myocardium who will benefit from revascularization. Once a diagnosis has been established, assessment for viable myocardium can be done using stress echocardiography; however, coronary angiography \pm angioplasty is the mainstay of diagnostic and therapeutic interventions.

Valvular cardiomyopathy

Patients with valvular heart disease will develop a cardiomyopathy that is dependent on the predominant valvular lesion. Significant improvement in cardiac function can often be seen after correction of the valve disease.

Hypertensive cardiomyopathy

Hypertension causes LVH in response to increased afterload, which is compensatory and protective to a point. However, there are ultimately detrimental effects on systolic and diastolic ventricular function. Hypertension also leads to accelerated atherosclerosis and ischaemic heart disease. Hypertensive cardiomyopathy is the commonest form of CCF outside the western world.

Alcoholic cardiomyopathy

Chronic alcohol excess is the commonest 2° cause of DCM in the western world. Proposed mechanisms include (1) a direct toxic effect of ethanol causing apoptosis and myocyte loss and acetaldehyde causing depressed myocardial contraction; (2) concomitant nutritional deficiencies (especially thiamine); and (3) rarely, toxic effects of additives (cobalt). Progression to alcoholic cardiomyopathy is related to the mean daily alcohol intake and total duration of drinking (approximately 1 L of wine every day for 5 years). Clinical presentation, diagnosis, and treatment are similar to DCM. However, unlike other forms of DCM, abstinence from alcohol early in the disease process may stop progression, or even result in significant improvement in cardiac function.

Metabolic cardiomyopathy

Various abnormalities in metabolism can result in cardiomyopathy. As already mentioned, lysosomal and glycogen storage diseases can cause a form of restrictive cardiomyopathy. Haemochromatosis also causes restrictive cardiomyopathy by unknown mechanisms. Acquired errors of metabolism such as acromegaly result in biventricular hypertrophy. Diabetes mellitus can cause cardiomyopathy with systolic and/or diastolic dysfunction, even in the absence of significant epicardial CAD.


Takotsubo cardiomyopathy

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, or transient apical ballooning syndrome, is a rare but increasingly recognized cardiac syndrome. It is characterized by transient systolic dysfunction of the apical and/or mid segments of the left ventricle, with a compensatory hyperkinesis of the basal walls producing ballooning of the apex during systole. The condition is more prevalent in postmenopausal women and is often triggered by intense emotional or physical stress (e.g. bereavement, domestic abuse, natural disasters).

The clinical presentation of takotsubo cardiomyopathy is similar to acute MI, with retrosternal chest pain, ST segment elevation and raised cardiac biomarkers. Other features may include tachy- and bradyarrhythmias, signs of left ventricular failure, transient LVOT obstruction, and even cardiogenic shock. Coronary angiography, by definition, reveals no evidence of significant coronary stenosis. The diagnosis is reached by left ventriculography or transthoracic echocardiography (TTE), which identifies the characteristic apical ballooning with associated reduced left ventricular systolic function. The pathogenesis of takotsubo cardiomyopathy remains poorly understood; however, postulated mechanisms include catecholamine excess causing coronary artery spasm and microvascular dysfunction, or by direct catecholamine-mediated myocardial toxicity.


Management of this condition is essentially supportive, with IV hydration, treatment of complications, and attempts to alleviate any causative emotional or physical stress. The prognosis, in small studies, is good in those individuals surviving the acute episode, with recovery of normal left ventricular function within 4–6 weeks.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a form of DCM. Symptoms occur in the third trimester and the diagnosis is made in the peripartal period. Approximately half will show complete or near-complete resolution over the first 6 months post-partum. Of the remainder, some will continue to deteriorate and result in death or transplantation, while others continue to experience chronic CCF. Its diagnosis is established by excluding other causes of DCM, and the cause is unknown (also see  Chapter 15, Heart disease in pregnancy, p. 673).


Cardiomyopathy in systemic disease

Systemic lupus erythematosus (SLE) can cause heart disease in many ways. Approximately 10% of patients with SLE have evidence of myocarditis. Patients with associated antiphospholipid antibody syndrome have increased risk of valvular abnormalities and DCM due to thrombotic occlusions of the microcirculation without vasculitis. They also have increased atherogenesis.

Pulmonary hypertension due to pulmonary vasculitis is an uncommon cause of cardiomyopathy in patients with rheumatoid arthritis (see also  p. 618).

Nutritional cardiomyopathy

Thiamine is an important coenzyme in the hexose monophosphate shunt. Infants who are breast-fed in areas with diets deficient in thiamine develop mainly right ventricular failure between 1 and 4 months of age. Prompt correction of the vitamin deficiency results in rapid improvement in the cardiac abnormalities without long-term consequence.

Protein-calorie malnutrition (marasmus, kwashiorkor) results in thinning and atrophy of muscle fibres and ultimately DCM. Careful treatment may result in marked improvement over several months, provided the patient survives the initial period (see also  Chapter 14, Cardiovascular disease in less-developed countries, p. 653).

Sensitivity or toxic reactions

A large number of non-infectious agents can damage the myocardium. The damage can be acute, with evidence of an inflammatory reaction, or there may be no inflammation and necrosis as in hypersensitivity reactions. Other agents lead to chronic changes, with progressive fibrosis and an ultimate picture similar to DCM. Numerous chemical and industrial agents, radiation, and excessive heat can all cause myocardial damage.

Neuromuscular disorders

Cardiac involvement in Friedreich's ataxia is relatively common, although usually asymptomatic. Friedreich's ataxia is an autosomal recessive trait with loss of function of the frataxin gene. Clinical manifestations include progressive ataxia of all four limbs, diabetes mellitus, and cardiac disease. It is most commonly associated with HCM on electrocardiography and echocardiography but is distinct from the genetic variety by lack of myofibrillar disarray on histology. Serious ventricular arrhythmias and complications related to cardiomyopathy are the most frequent cause of morbidity. Rarely, it is associated with DCM.

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Muscular dystrophies

Muscular dystrophies (MDs) are a group of hereditary muscle disorders characterized by progressive skeletal muscle weakness. Over 100 conditions are associated with a muscular dystrophy, although the best characterized include Duchenne's and Becker's, limb-girdle, facioscapulohumeral, myotonic, oculo-pharyngeal, distal, and Emery–Dreifuss.

A significant number of types of muscular dystrophy are multisystem disorders, with effects on smooth muscle and cardiac muscle as well as skeletal muscle. The MDs can be inherited with an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance. They affect the myocardium and conduction tissue predominantly, causing varying degrees of heart block, tachyarrhythmias, and heart failure.

Symptoms can be very difficult to gauge, as affected patients are often limited by severe disability. Regular surveillance with 12-lead ECG, in the first instance, and a low threshold for echocardiography is important to identify cardiac involvement early. Once a diagnosis of cardiomyopathy is made, standard heart failure treatment with diuretics, ACE-Is, and β -blockers is required. Arrhythmias and symptoms of CCF secondary to DCM are a significant cause of morbidity and mortality in this group of patients.

Duchenne's (DMD) and Becker's (BMD) muscular dystrophy

are X-linked disorders of the dystrophin gene. DMD presents in childhood and is the commonest hereditary MD, with near-complete absence of the sarcolemmal membrane protein dystrophin. BMD presents in adulthood and is associated with less-severe skeletal muscle involvement but often more-severe cardiac muscle involvement. Cardiac abnormalities include conduction abnormalities of the AV node, and LV dysfunction that can be rapidly progressive.

Limb girdle muscular dystrophy (LGMD) affects the shoulder and pelvic girdle muscles and can be inherited in an autosomal dominant or recessive pattern. Mutations occur in genes encoding proteins of the nuclear envelope in skeletal muscle. Cardiac involvement is particularly predominant in LGMD1B (laminopathy), LGMD1D, LGMD2E, and LGMD2I, with cardiomyopathy and conduction-system disease.

Facioscapulohumeral muscular dystrophy (FSH) is an autosomal dominant MD with progressive involvement of the facial, shoulder, and hip girdle muscles. Cardiac manifestations include P-wave abnormalities, interventricular conduction delay, and supraventricular arrhythmias.

Myotonic dystrophy is an autosomal dominant multisystem disease caused by a trinucleotide repeat defect in the gene encoding myotonin. It is associated with AV conduction abnormalities, atrial and ventricular arrhythmias, and rather than cardiomyopathy in ~10% of cases. SCD from any cause is seen in up to 30% of patients with myotonic dystrophy.

Emery–Dreifuss MD has a variable pattern of inheritance and is caused by mutations in lamin A and lamin C (nuclear envelope proteins). Muscle weakness has a humeral and peroneal distribution, with multiple contractures often being a feature. Cardiac manifestations include AV conduction abnormalities and atrial arrhythmias. SCD due to ventricular tachyarrhythmia can occur.

Myocarditis

Myocarditis is the process whereby the myocardium becomes inflamed by one of a large range of infectious agents. Unfortunately, the infectious agent is rarely identified. Numerous bacteria, viruses, spirochetes, fungi, parasites, and rickettsia can cause myocarditis.

Aetiology

Damage can result from a number of mechanisms, including a direct toxic effect on the myocyte, production of a toxin (e.g. diphtheria), and immunologically mediated cell damage. Histological findings depend on a number of factors, including the infectious agent, stage of disease, and mechanism of damage. Damage can be focal or diffuse, and is randomly distributed throughout the myocardium.

Symptoms

The clinical consequences of the damage can range from asymptomatic subclinical infection to rapidly progressive and ultimately fatal CCF.

Long-term consequences are also variable. Patients who were initially asymptomatic can present after a prolonged latency period with DCM or have complete recovery. Patients who present early, even with fulminant CCF, can also have complete recovery. Patients with non-fulminant presentations can gradually deteriorate or recover gradually.

Diagnosis


The diagnosis is often established by identifying the associated systemic illness. Isolation of the infectious agent is rarely achieved, although clearly supportive of the diagnosis if positive. Endomyocardial biopsy can be useful in confirming the diagnosis but is frequently negative.

Treatment

Management of patients with myocarditis is largely supportive. Physical activity should be restricted, as in animal models exercise was found to be detrimental to cardiac function. Standard management of CCF and eradication of the infectious agent are the mainstay of treatment. Symptomatic arrhythmias should be controlled, and β -blockers may be cardioprotective.

Trials of immunosuppressive therapy in patients with myocarditis have been largely disappointing. The use of steroids in acutely ill patients could be considered but any benefit is unproven.

Viral myocarditis

- In western countries, the enterovirus (especially Coxsackie B) is the commonest cause of myocarditis. This is usually mild and self-limiting, although it can be particularly virulent in neonates and young children. Clinical manifestations in adults include myalgia, pleuritic chest pains, upper respiratory tract symptoms, arthralgia, palpitations, and fever. The ECG is usually abnormal with ST- and T-wave changes, VEs, and AV conduction abnormalities. Cardiac enzymes may be elevated or normal, reflecting the degree of myocardial necrosis. Echocardiography may show diffuse or regional LV dysfunction. Most make an uneventful recovery within weeks. Treatment is symptomatic.
- Other viruses such as cytomegalovirus (CMV), Dengue, hepatitis, Epstein–Barr virus (EBV), influenza, and varicella are rarely associated with cardiac involvement. ECG changes and cardiac enzyme release makes the diagnosis. With mumps, myocarditis is rarely recognized, but pathologically, it is common. Myocarditis generally occurs in the first week of illness and is transient. Rubella infection in the 1st trimester of pregnancy results in congenital lesions such as patent ductus or pulmonary artery maldevelopment; myocarditis is rare but causes fetal/neonatal heart failure.
- Cardiac involvement is common in patients with human immunodeficiency virus (HIV; up to 50%) but only clinical evident in 10%. The usual presentation is with CCF and DCM, due to a direct effect of HIV on the myocardium, although opportunistic infection in acquired immune deficiency syndrome (AIDS) patients is another important cause of myocarditis (see also  HIV and the cardiovascular system, p. 658).

Rickettsial myocarditis

- Q fever (*R. burnetti*) typically causes endocarditis; pericarditis (chest pain and dyspnoea) is also common. Myocarditis is uncommon and produces ECG changes such as transient ST- and T-wave changes).
- Rocky Mountain spotted fever (*R. rickettsii*) produces a widespread vasculitis that involves the myocardium. ECHO shows unexpected LV dysfunction, which may persist even after the infection is cleared.
- Scrub typhus (*T. tsutsugamushi*) produces a panvasculitis that may involve the myocardium, producing haemorrhage into the myocardium and subepicardial petichiae. Long-term damage appears to be infrequent.


Bacterial myocarditis

- *Diphtheria*: myocarditis occurs in up to 20% and is due to the production of a toxin that inhibits protein synthesis. Clinical signs appear towards the end of the first week of infection with CCF, and cardiomegaly. ECG changes are seen and may persist after recovery. Treatment with antitoxin should be given early in the course of the disease. Corticosteroids do not appear to be helpful. However, treatment with carnitine seems to reduce the incidence of heart failure and need for pacemaker, and lowers mortality.
- *Meningococcus*: myocarditis is associated with increased mortality, and results in haemorrhagic lesions and intracellular organisms. Clinical features include CCF and an pericardial effusion with tamponade. Patients with septicaemia should be monitored, especially if there are ECG abnormalities.
- *Mycoplasma*: ECG changes are not uncommon in patients with mycoplasma pneumonia. Other manifestations include pericarditis and CCF. No specific treatment for the carditis is usually indicated.
- *Whipple's disease*: (*Tropheryma whippelli*) may involve the myocardium with infiltration with periodic acid–Schiff (PAS)-positive macrophages. Coronary artery lesions may be seen. Pulmonary arterial hypertension can occur. Valve fibrosis produces aortic and mitral regurgitation. Antibiotic therapy appears to be effective, but relapses are not uncommon.
- Other bacterial infections occasionally associated with cardiac involvement include legionella, salmonella, psittacosis, and Streptococcus (see [Acute rheumatic fever](#), p. 146). Tuberculous myocarditis is rare unless there is pericarditis (see [Tuberculous pericarditis](#), p. 468).


Spirochetal myocarditis

- About 10% of patients with *Lyme disease* (caused by the tick-borne spirochete *Borrelia burgdorferi*) have evidence of cardiac involvement—a combination of direct muscle invasion by the spirochete together with immune-mediated damage. Although this normally takes the form of AV-conduction abnormalities, LV dysfunction can be present. Syncope due to complete heart block is frequent, and there are often associated ventricular escape rhythms. VT is uncommon. A positive gallium or indium antimyosin antibody scan may point toward suspected cardiac involvement. Patients with 2nd- or 3rd-degree heart block require hospital admission and monitoring. Treatment is with IV penicillin, and temporary pacing (if required). The role of steroids and aspirin is unclear.
- *Leptospirosis* (Weil disease): cardiac involvement is seen in the more severe presentations. Interstitial myocarditis with involvement of the papillary muscles is seen; conduction defects, aortitis, and coronary arteritis have been described.
- *Syphilis* most commonly produces an aortitis, and direct involvement of the myocardium with gummae is rare (see [Cardiovascular syphilis](#), p. 662).


Protozoal myocarditis

- In South America, the parasite *Trypanosoma cruzi* causes the myocarditis Chagas' disease, which is a significant public health problem (see  Chagas' disease, p. 660). In the acute phase, it can cause severe myocarditis resulting in CCF and death. Histologically, parasites can be seen lying alongside the myofibres. Immune lysis by antibody- and cell-mediated immunity directed against *T. cruzi* antigens adsorbed onto the myocardium appears to be the mechanism of damage. Young children more commonly develop the acute disease and are more severely affected than adults.
- After an average of 20 years, ~30% of patients develop findings of chronic Chagas' disease. Clinical manifestations vary from asymptomatic seropositivity to progressive cardiac chamber dilatation, with resultant severe CCF. AV conduction defects also occur. Histologically, there is extensive fibrosis but no parasites are seen. Fatigue, peripheral oedema, ascites, and hepatomegaly are seen. Ventricular arrhythmias are common: multifocal VEs and bouts of VT occur, culminating in syncope and SCD. ECHO shows features of dilated cardiomyopathy; in advanced cases, the appearances are distinctive, with posterior hypokinesis with relatively preserved septal motion.
- Diagnosis is with the complement fixation test (Machado–Guerreiro), indirect immunofluorescence, or enzyme-linked immunosorbent assay (ELISA). Treatment is supportive; amiodarone is useful for ventricular arrhythmias; anticoagulation prevents thrombolism. Antiparasitic agents reduce parasitaemia, but there is no evidence that they cure the disease.
- Myocardial involvement with other protozoa (e.g. trypanosomes, toxoplasma, or malaria) is rare and usually asymptomatic. Severe fatal disease is occasionally seen.

Fungal myocarditis

- Fungal infection is rare and seen in patients with concomitant malignant disease or those receiving chemotherapy, steroids, or other immunosuppressive therapy. Other predisposing factors include cardiac surgery, HIV infection, and IV drug use.
- Organisms implicated include *Actinomyces*, *Aspergillus*, *Candida*, *Cryptococcus*, and *Histoplasma*. Generalized coccidioidomycosis generally causes epicardial lesions with pericarditis, progressing on to constrictive pericarditis (see  Constrictive pericarditis, p. 464). Myocardial involvement has been described.

Toxic and metabolic myocarditis

A variety of drugs, chemical agents, and physical agents (e.g. radiation, heat) may result in myocardial damage. Cardiac involvement in systemic disease is discussed in  Chapter 13, Multisystem disorders, p. 617.

Anthracyclines (daunorubicin and adriamycin): These drugs inhibit nucleic acid synthesis and can produce acute and late toxicity. Acute cardiotoxicity includes arrhythmias, acute LV dysfunction, a pericarditis-myocarditis syndrome, MI, and SCD. Late cardiotoxicity is due to a dose-dependent degenerative cardiomyopathy that manifests anywhere from weeks to months after the last dose. Symptoms can be difficult to control, and cardiac transplantation has been used in cases where 'cancer cure' has been achieved.

Cocaine: This produces chest pain, sweating, and palpitations. In a minority there is myocardial ischaemia due to coronary vasoconstriction or thrombotic occlusion of the coronary. Associated findings include ventricular arrhythmias, and SCD. Treatment is supportive and with β -blockers.

Catecholamines: Severe reversible dilated cardiomyopathy has been described with pheochromocytoma, as well as treatment with high doses of catecholamines and excessive doses of β -agonists in decompensated pulmonary disease. Aspirin and dipyridamole may offer some protection, suggesting a role for platelets in the pathogenesis.

Carbon monoxide: Poisoning usually results in central nervous system (CNS) depression, but subendocardial myocardial necrosis is seen. Palpitations, sinus tachycardia, AF, and ventricular arrhythmias may be seen. ECG abnormalities are common. Treatment with 100% oxygen, bed rest, and supportive treatment for arrhythmias is usually effective.

Electrolyte abnormalities: Chronic hypocalcaemia is associated with CCF that only responds to restoration of serum calcium. Rapid blood transfusion (citrate blood) has been described to result in transient LV dysfunction, due to low serum calcium levels. Severe hypophosphataemia can also result in reversible LV impairment, restored by correcting the phosphate levels. Hypomagnesaemia is associated with SVT and VT (especially in the context of digitalis toxicity), and focal myocardial necrosis is seen.

Deficiency of taurine and carnitine: Is associated with a DCM, and in the case of carnitine, supplementation can lead to symptomatic and functional improvement. Myocardial carnitine levels are reduced in patients with DCM but the significance of this is still debated. Selenium deficiency accounts for a type of DCM seen in parts of rural China, and is occasionally seen in patients on total parenteral nutrition (TPN) without selenium supplements.

Hypersensitivity myocarditis (eosinophilia and myocardial infiltraton with eosinophils and giant cells) has been described with a variety of drugs, including antibiotics (penicillins, amphotericin, chloramphenicol, tetracycline, sulphonamides), anti-epileptics (phenytoin, carbamazepine), antituberculous drugs (isoniazid), non-steroidal anti-inflammatory drugs (NSAIDs; indomethacin, phenylbutazone), diuretics (spironolactone, hydrochlorothiazide, acetazolamide), sulphonylureas, and amitryptiline. It is rarely recognized clinically. The offending drug should be stopped, and steroids may be required in severe cases.

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Pericardial diseases

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Aetiology

The pericardium may be involved in the large number of disease processes listed in the box below. In some patients, pericardial disease is the primary disease process dominating the clinical picture, whereas in others it is a manifestation of a systemic disease. The most common causes are idiopathic, viral, uraemic, neoplastic, tuberculous pericarditis, and acute myocardial infarction (MI). The spectrum of pericardial disease is determined by the age and social circumstances of the patient. In an elderly North American and Western European population, the commonest causes are malignancy, followed by uraemia and MI. In less privileged communities and in developing countries, tuberculosis (TB) is still the predominant cause of pericardial disease.

Causes of pericardial disease

- **Infections**
 - bacterial: *Mycobacterium tuberculosis*, *Staphylococcus*, *Pneumococcus*, *Meningococcus*, *Mycoplasma*
 - viral: Coxsackie, cytomegalovirus (CMV), ECHO, Epstein–Barr virus (EBV), influenza, human immunodeficiency virus (HIV), mumps, Parvo B19, rubella, varicella
 - fungal: histoplasmosis, blastomycosis
 - parasitic: amoebiasis
- **Autoimmune and hypersensitivity diseases**
 - collagen vascular diseases: systemic lupus erythematosus, polyarteritis nodosa, scleroderma, dermatomyositis
 - type 2 autoimmune disorders: rheumatic fever, autoreactive pericarditis, post-MI and postpericardiectomy syndromes
 - drug-induced: hydralazine, procainamide, penicillin, phenylbutazone
 - other autoimmune disorders: rheumatoid arthritis, ankylosing spondylitis
- **Pericardial involvement by disease in surrounding organs**
 - heart: acute MI, myocarditis
 - lung: pulmonary infarction, pneumonia
- **Malignant disease**
 - primary: mesothelioma, sarcoma, fibroma, lipoma
 - secondary: lung carcinoma, breast carcinoma, melanoma, lymphoma, leukaemia
- **Bleeding into the pericardium**
 - trauma: penetrating and non-penetrating
 - dissecting aortic aneurysm
 - haemorrhagic diathesis: leukemia, scurvy
 - anticoagulants: warfarin
- **Metabolic disorders**
 - uraemia, dialysis-related, myxoedema, gout
- **Miscellaneous**
 - acute idiopathic pericarditis, radiation, sarcoidosis, amyloidosis, familial Mediterranean fever


Syndromes of pericardial disease

Pericardial reaction to the various disease processes is limited, and we are thus able to distinguish five clinical and pathological forms of pericarditis:

- acute pericarditis without effusion
- pericardial effusion with or without tamponade
- constrictive pericarditis
- effusive-constrictive pericarditis
- calcific pericarditis without constriction.

Acute pericarditis without effusion

(‘Dry’ pericarditis)

Aetiology: Any of the causes listed in the box on  Aetiology, p. 460 may cause dry pericarditis. The clinical syndrome is commonly seen in acute viral pericarditis or after MI.

Pathology: There is a fibrinous exudate with an inflammatory reaction involving the visceral and parietal pericardium. The epicardium is also involved and this accounts for the electrocardiography (ECG) changes that are seen, and the rise in cardiac enzymes (e.g. troponin I).

Symptoms: Sharp, stabbing, central chest pain is common, with radiation to the shoulders and upper arm. It is relieved by sitting up and leaning forward, and aggravated by lying down, and may be accentuated by inspiration, cough, swallowing, or movement of the trunk. Fever, night sweats, and other constitutional symptoms may be present, depending on the underlying cause.

Signs: A pericardial friction rub is frequently heard. This is a superficial, scratchy, grating sound that is best heard in the second to fourth intercostal spaces when pressure is exerted on the diaphragm of the stethoscope. Positioning the patient leaning forward and listening in held inspiration may bring it out. The rub is classically described as being triphasic. Usually you hear at least two components due to atrial systole and ventricular systole. Occasionally, a third component attributed to rapid ventricular filling is heard.

ECG: The patient is usually in sinus rhythm but atrial fibrillation (AF) may occur. In the early stages there is widespread ST segment elevation with concavity directed upwards, and PR segment deviation opposite to the polarity of the P wave. After a few days the ST segments, followed by PR segments, return to normal, and T waves become inverted.


Chest X-ray (CXR): The cardiac shadow is not enlarged in dry pericarditis.

Differential diagnosis: Acute pericarditis must be differentiated from MI, spontaneous pneumothorax, and pleurisy.

Diagnosis of acute pericarditis is based on typical symptoms of chest pain, pericardial rub, and/or characteristic ECG changes.

Management: Treat the underlying cause. Good pain relief can be achieved by the use of non-steroidal anti-inflammatory agents (NSAIDs).

Pericardial effusion with or without tamponade

Aetiology: Any of the causes listed in the box on  Aetiology, p. 460 may cause pericardial effusion. Large effusions are common with neoplasia, TB, uraemic pericarditis, and myxoedema.

Pathology: In addition to fibrinous inflammation, there is significant fluid exudation. The pericardial fluid may be serous, sero-sanguineous, haemorrhagic, or purulent, depending on the underlying cause. Haemorrhagic effusion is common in TB or neoplasia. Brownish fluid with an anchovy-sauce appearance is highly suggestive of amoebic pericarditis.

Clinical features: The clinical presentation varies, depending on the rate of accumulation of the fluid, the amount of fluid that accumulates, and the stage at which the patient is first seen.

Symptoms: Chest pain may be typically pericardial (as described under dry pericarditis), or it may be dull and heavy due to distension of the pericardium. Dyspnoea is common, and orthopnoea may occur later in the course of the disease. Cough may be present due to compression of surrounding structures. Constitutional symptoms may be present, depending on the cause of the disease.

Signs: Typically, praecordial dullness extends beyond the apex beat (which may be impalpable), and dullness is present to the right of the sternum. Dullness and bronchial breathing at the left base posteriorly may be found, due to compression of the left lower lobe bronchus (Ewart's sign). Cardiac tamponade should be considered in a patient with hypotension, raised jugular venous pressure (JVP), and quiet heart sounds (Beck's triad). The primary defect in cardiac tamponade is interference with diastolic filling of the heart. The other clinical features of cardiac tamponade are the presence of tachycardia, pulsus paradoxus (fall in systolic blood pressure on inspiration of >10 mmHg or inspiratory fall in systolic blood pressure that exceeds half the pulse pressure), elevated JVP with brisk 'x' descents and absent 'y' descents, rise in JVP on inspiration (Kussmaul's sign), dyspnoea or tachypnoea with clear lungs, and hepatomegaly.

ECG: Sinus tachycardia, generalized low-voltage QRS complexes with non-specific ST segment and T-wave changes. Electrical alternans, involving the QRS complex, suggests the presence of a massive pericardial effusion. Total electrical alternans (P-QRS-T), which is uncommon, is pathognomonic of cardiac tamponade.

Echocardiography: Is diagnostic, showing an ECHO-free zone surrounding the heart. The fluid may not be evenly distributed. Diastolic collapse of the right ventricle and right atrium indicate cardiac tamponade. The following features are more common in patients with tuberculous or malignant causes of pericardial effusion: soft tissue density masses, thickening of the visceral pericardium, and presence of fibrinous strands. The hallmark of benign, idiopathic effusion is a clear ECHO-free space, whereas malignancy, bacterial infection, and haemorrhagic effusions are more likely to have solid components or stranding.



CXR: Shows a large globular heart, usually with clear lung fields.

Cardiac catheterization: Establishes the diagnosis and severity of tamponade. The important findings are:

- equilibration of mean right atrial, right ventricular end-diastolic, and mean capillary wedge pressure
- rapid 'x' descent on the right atrial pressure waveform
- pulsus paradoxus.

Differential diagnosis: Myocardial infarction and pulmonary embolism.

Management

- When an effusion does not cause haemodynamic impairment and the cause is known (e.g. uraemia, myxoedema), then no further investigations are necessary and the treatment consists of treating the underlying cause.
- If the cause is not known, then pericardiocentesis must be considered. Aspiration of the fluid helps to establish the nature of the effusion (see  Pericardial fluid analysis, p. 476).
- Cardiac tamponade is a life-threatening condition: urgent pericardial aspiration is necessary (see  pp. 814–6). Surgical drainage is indicated for haemopericardium or purulent pericarditis.

Constrictive pericarditis

Aetiology: Constrictive pericarditis is usually due to TB. Other causes are mediastinal irradiation, purulent pericarditis, previous trauma (surgical or non-surgical) with infection of the pericardial space, and, very rarely, viral pericarditis.

Pathology: The pericardium becomes a dense mass of fibrous tissue and this may be calcified. This results in encasement of the heart within a non-expansile pericardium.

Symptoms: Dyspnoea, oedema and abdominal swelling due to ascites and hepatomegaly.

Signs: Small volume pulse and pulsus paradoxus. JVP is always elevated, usually very high with prominent 'x' and 'y' descents. A diastolic knock is usually felt at the left sternal border due to the sudden halting of the ventricles during diastolic filling. The apex beat may be impalpable. Heart sounds are usually soft, and an early third sound coincident with the diastolic knock is usually heard. In the pulmonary area there is sudden instantaneous widened splitting of the second sound that occurs following the first heartbeat of inspiration (Vogelpoel–Beck sign). The liver is commonly grossly enlarged, ascites is marked, and peripheral oedema is present.

ECG: Is abnormal in virtually every case, but changes are non-specific. (i.e. generalized low-voltage QRS complexes, and widespread flattening and inversion of T waves). AF is common in the chronic form.

CXR: A normal or near-normal cardiac size in the presence of marked venous distension or heart failure is suggestive of constrictive pericarditis or restrictive cardiomyopathy. Pericardial calcification is diagnostic but its incidence varies from 5% to 70% of cases in different series.

Echocardiography: Pericardial thickening may be present. There is a restrictive mitral filling pattern on Doppler, with respiratory variation of >25% over the AV valves.

Computed tomography (CT) and magnetic resonance imaging (MRI) scan: These techniques demonstrate pericardial thickening (>5 mm).

Cardiac catheterization: This demonstrates elevation and equalization of filling pressures. In the typical case, the difference in filling pressures between the right ventricle and left ventricle does not exceed 6 mmHg. The right atrial waveform shows rapid 'x' and 'y' descents, and the mean pressure does not decrease normally with inspiration, or may show Kussmaul's sign.

Management: Constrictive pericarditis is treated by surgical removal of the fibrous constrictive tissue (pericardiectomy).

Effusive-constrictive pericarditis

Aetiology: This is characteristically encountered in active TB pericarditis, where there are signs of both pericardial effusion or tamponade and constriction. It may also occur in neoplastic, radiation, and septic pericarditis.

Clinical presentation: Symptoms are usually those of constriction. Examination reveals pulsus paradoxus, raised JVP with prominent 'x' and 'y' descents. The CXR shows an enlarged cardiac silhouette like that of pericardial effusion.

Diagnosis: The clue to diagnosis is persistent signs of constriction following adequate pericardial drainage.

Management: Treatment of the underlying cause and pericardial drainage is indicated. Pericardiectomy is indicated should haemodynamics not improve.


Calcific pericarditis without constriction

This condition is usually discovered during routine radiological examination, which demonstrates pericardial calcification. There are no symptoms and signs of constriction, and the cause is usually unknown.

Viral pericarditis

Clinical presentation: Most patients present with a history of upper respiratory tract infection within the preceding three weeks. The viruses most frequently responsible include Coxsackie B, ECHO, mumps, influenza, and varicella. Pericardial pain, fever, and malaise are typical. The physical examination reveals a pericardial friction rub and/or characteristic changes of acute pericarditis on ECG.

Course: In the majority of patients, the illness resolves spontaneously in one to two weeks. In some patients, the illness recurs on at least one occasion in the next few weeks or months, and in 20% of patients there are multiple recurrences in the ensuing months or years (benign relapsing pericarditis).

Diagnosis: It is important to search for an underlying disease (see the box on  Aetiology, p. 460) that may require specific therapy. In most cases of suspected viral pericarditis, special studies for aetiological agents are not necessary because of the low diagnostic yield of viral studies and lack of specific therapy for viral disease.

Treatment: NSAIDs are effective in most patients with viral pericarditis. There are no data from randomized controlled trials to guide treatment for relapsing patients who do not respond to NSAIDs. Corticosteroids (prednisone 1–1.5 mg/kg for at least 1 month) provide symptomatic relief in most patients; symptoms recur in many patients when the prednisone dose is reduced. Colchicine (2 mg/day for 1–2 days, followed by 1 mg/day) may be effective when NSAIDs and corticosteroids fail to prevent relapses. If patients do not respond adequately, azathioprine (75–100 mg/day) or cyclophosphamide may be added. Pericardiectomy is indicated only in frequent and highly symptomatic recurrences that are resistant to medical therapy. However, postpericardiectomy recurrences may occur, possibly due to incomplete resection of the pericardium.

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Tuberculous pericarditis

Tuberculous pericarditis is uncommon in the first world, but is very common in developing countries, and the incidence appears to be increasing in sub-Saharan Africa in parallel with the HIV/AIDS (acquired immune deficiency syndrome) epidemic. The disease presents in three forms: pericardial effusion, constrictive pericarditis, and effusive-constrictive pericarditis.

Tuberculous pericardial effusion

Pathology: Pericardial effusion is the commonest mode of presentation, with or without tamponade. The effusion is bloodstained in over 95% of cases, and may even resemble venous blood. The absence of parenchymal lung disease and the presence of hilar lymphadenopathy in many of these patients suggest a direct spread from a TB hilar node to the pericardium.

Clinical presentation: Systemic symptoms are variable. Typical pericardial pain is uncommon and the classic ECG features of pericarditis are uncommon. CXR shows an enlarged globular heart, small pleural effusions on one or both sides, and evidence of pulmonary TB in about 30% of cases. The echocardiogram shows features of pericardial effusion, typically associated with soft tissue density masses, thickening of the visceral pericardium, and fibrinous strands.

Diagnosis: A *definite diagnosis* of TB pericarditis is based on the demonstration of tubercle bacilli in the pericardial fluid or on histologic section of the pericardium. Pericardial effusion should be investigated by pericardiocentesis. Fluid should be sent for microscopy (to identify acid-fast bacilli (AFB)) and culture of *Mycobacterium tuberculosis*. The chances of a positive culture are improved by bedside inoculation of the fluid into double-strength Kirschner culture medium. Pericardial biopsy and drainage offer the advantage of a histological diagnosis and early complete drainage of the pericardium. This can be performed via the sub-xiphisternal approach under local anaesthesia.

A *probable diagnosis* is made when there is proof of TB elsewhere in a patient with unexplained pericarditis. Palpation in the supraclavicular fossa will frequently reveal enlarged lymph nodes, which should be biopsied. AFB-positive sputum will only be found in about 10% of cases. Tuberculin skin testing is of little value in endemic and non-endemic areas. It is not known whether the enzyme-linked immunospot (ELISPOT) test that detects T cells specific for *M. tuberculosis* antigen will perform better in TB pericarditis than the tuberculin skin test.

Several tests have been developed for the rapid diagnosis of TB in the pericardial fluid. Polymerase chain reaction (PCR) can identify DNA of *M. tuberculosis* rapidly from only 1 μ L of pericardial fluid (sensitivity 75%, specificity 100%). An adenosine deaminase (ADA) level >40 U/L has a sensitivity of 83% and a specificity of 78%. A high interferon G level is also a highly sensitive (92%) and specific (100%) marker of pericardial TB.

Treatment: Is by means of standard four-drug anti-TB chemotherapy for 6 months. Overall mortality ranges from 17% to 40%, with HIV-infected individuals having a worse outcome than HIV-negative patients. Repeat pericardiocentesis is required in about 15% of patients, and during a two-year follow-up period, about 10% of patients will require pericardiectomy.

While some favour the addition of steroids to conventional therapy, their role in improving survival is not clearly established, particularly in HIV infection.

Tuberculous pericardial constriction

Clinical presentation: Most cases have an active inflammatory fibrocaseous tissue surrounding the heart, and involving visceral and parietal pericardium. The clinical presentation is highly variable. Patients range from being asymptomatic to severe signs and symptoms of constriction. The diagnosis is often missed on cursory clinical and echocardiographic examination. It is uncommon to find concomitant pulmonary TB, and pericardial calcification is found in <5% of cases.

Treatment: The initial management of patients with non-calcific TB constrictive pericarditis is with anti-TB therapy, and since the process is an active fibrocaseous condition, resolution of constriction occurs in 15–20% of patients with medical management over 3–4 months. Pericardiectomy is recommended if no improvement has occurred after 6 weeks of anti-TB treatment, or improvement is unsatisfactory after several months of treatment. By contrast, calcific TB pericarditis is treated by early pericardiectomy and anti-TB chemotherapy.

Effusive-constrictive tuberculous pericarditis

Features: This mixed form is a common presentation of TB pericarditis. There is increased pericardial pressure due to effusion in the presence of visceral constriction. The echocardiogram shows porridge-like exudation, with loculation of the fluid.

Treatment: Is by standard four-drug therapy. The role of adjuvant steroids is not known. The mortality is about 10%, and about 30% of cases will come to pericardiectomy over two years of follow-up.

Uraemic pericarditis

Pathology: Uraemia produces a fibrinous, often haemorrhagic inflammation that may lead to tamponade, and constriction in some cases.

Management: Symptomatic pericarditis that occurs before the initiation of dialysis will respond to repeated peritoneal dialysis or haemodialysis. Heparin-free haemodialysis should be used to avoid haemopericardium. Many patients who develop pericardial effusion while on dialysis (dialysis-associated pericarditis) will respond to intensification of the dialysis regime. Those who do not respond will require drainage by either subxyphoid pericardiotomy or pericardial window. Pericardiocentesis is associated with a high risk of intrapericardial haemorrhage.

Neoplastic pericardial disease

Aetiology: Usually secondary to malignancy of the bronchus, breast, or kidney. Primary tumours of the pericardium are rare and usually a result of mesothelioma following asbestos exposure.

Diagnosis: Metastases may produce a large haemorrhagic effusion or severe constriction when tumour encases the heart. Malignant cells may be found in 85% of cases of aspirated pericardial fluid. Tumour markers such as carcinoembryonic antigen (CEA), alpha-feto protein (AFP), and carbohydrate antigens (e.g., CA125) have been used in the diagnosis of malignant effusion. The differentiation of TB and neoplastic effusion is virtually absolute, with low adenosine deaminase (ADA) and high CEA levels in the latter.

Management: Depends on the type and stage of malignancy, condition of the patient, and presence of cardiac compression. Pericardiocentesis is effective in relieving neoplastic cardiac tamponade in the vast majority of cases. Commonly, neoplastic pericardial disease is a preterminal event. Palliation for recurrent tamponade can be obtained by subxyphoid surgical pericardiectomy (which can be performed under local anaesthesia), or by percutaneous balloon pericardiectomy to create a pleuro-pericardial window to allow fluid drainage into the pleural space in large malignant pericardial effusions in patients with a limited life expectancy. Partial pericardiectomy (pericardial window) through a left thoracotomy should be reserved for patients who have a better prognosis and are likely to respond to chemotherapy or radiation.

Intrapericardial instillation of cytostatic/sclerosing agents has also been used to prevent recurrences of large pericardial effusion. Intrapericardial treatment related to the type of tumour indicates that cisplatin may be effective in secondary lung cancer, and thiotepa may be effective in metastatic breast cancer. Tetracycline as a sclerosing agent controls malignant pericardial effusion in up to 85% of cases, but side-effects such as fever, chest pain, atrial arrhythmias, and constriction in long-term survivors are common.

Myxoedematous effusion

Clinical presentation: Effusion with high protein content is common in untreated myxoedema. Myxoedema must always be excluded in a patient with chronic, asymptomatic, pericardial effusion, associated with bradycardia, low voltage of the QRS complexes, and a history of radiation-induced thyroid dysfunction. Cardiac tamponade does not occur.

The diagnosis: Of hypothyroidism is based on serum levels of thyroxine and thyroid-stimulating hormone.

Treatment: With thyroid hormone causes resolution of the pericardial effusion.

Non-tuberculous bacterial (purulent) pericarditis

Predisposing conditions: Immunosuppression (e.g. immunosuppressive drugs, lymphoma, or HIV/AIDS); pre-existing pericardial effusion; cardiac surgery; and chest trauma. Children—pharyngitis, pneumonia, otitis media, endocarditis, and arthritis.

Precipitating factors: Cardiac surgery, pericardial aspiration, extension of aortic root endocarditis into the pericardial sac, or haematogenous spread from a septic focus such as osteomyelitis or pneumonia.

Causative organisms: Adults—*Staphylococcus aureus*, *Streptococcus pneumoniae*, Gram-negative bacilli, and anaerobes. Children—*Haemophilus*, *Staphylococcus aureus*, and *Neisseria meningitidis*.

Clinical presentation: Rare in adults without HIV infection. Presents as an acute, fulminating infectious illness and is fatal if not treated. The most important reason for this poor outlook is failure to suspect the condition in debilitated patients with overwhelming systemic infection.

Diagnosis: Pericardiocentesis shows purulent fluid, with high white cell count, low glucose, positive Gram stain for organism, and positive pericardial fluid and blood culture.

Treatment: Complete pericardial drainage, preferably through a subxyphoid pericardiotomy, and systemic antibiotic therapy. The mortality rate is 40% even with appropriate management.

Radiation pericarditis

This usually follows treatment for lymphoma and breast cancer. The incidence of pericarditis depends on how much the heart is included in the field of radiation, the dose, the duration of treatment, and the age of the patient. Radiation is a common cause of effusive-constrictive pericarditis and may also result in myocarditis and premature coronary atherosclerosis.

Clinical evidence of pericarditis may occur during, or shortly after treatment, but is more usually delayed for approximately 1 year. The presentation is one of pericarditis with some effusion. In about 50% of cases there is evidence of tamponade, which requires drainage. Up to 20% of patients will require pericardiectomy because of severe constriction. The operative mortality is high (21%) and the postoperative 5-year survival is very low (1%), mostly due to underlying myocardial fibrosis and severe thickening of the visceral pericardium.

Drugs and toxins

Aetiology: Pericardial reactions to drugs and toxins are rare. Pericarditis may develop as part of the lupus erythematosus-like syndrome (hydralazine, isoniazid, procainamide, methyldopa, reserpine), hypersensitivity reaction (sodium cromoglicate, penicillins, streptomycin), serum sickness, or envenomation (scorpion fish sting).

Management: Consists of removal of the causative agent and symptomatic treatment.

Postcardiotomy syndrome

Clinical presentation: The syndrome occurs in approximately 30% of patients undergoing any form of cardiac surgery. It is more common in patients receiving aminocaproic acid during the operation. After a latent period of 2–3 weeks, there is fever, pericarditis, pleuritis, and pneumonitis, with a marked tendency to relapse. Dry pericarditis or pericarditis with effusion may occur. The illness is self-limited and varies in intensity and duration, but usually lasts only 2–4 weeks.

Treatment: NSAIDs, analgesics such as aspirin or colchicine. Steroids (oral or intrapericardial) induce prompt relief of symptoms, but should be reserved for severely affected patients, since relapse may occur when they are discontinued and dependency may result. Anticoagulants should be avoided because of the risk of haemopericardium.

Post-infarction pericarditis

Clinical presentation: Two forms of post-infarction pericarditis may be distinguished: (1) the usual early form of pericarditis occurs within a week in at least 20% of patients with transmural MI. It is a result of pericardial irritation by adjacent infarcted myocardium; (2) less commonly, a delayed autoimmune reaction may produce pericarditis 2 weeks to a few months after the infarct (Dressler syndrome). The delayed form behaves very similarly to the postcardiotomy syndrome.

Treatment: Ibuprofen is said to increase coronary flow, and is the NSAID of choice. Aspirin, up to 650 mg every 4 hours for 2–5 days, has also been used successfully. Occasionally, steroids may be required for relapse, but should be avoided as they may delay myocardial healing. Anticoagulants should be avoided because of the risk of haemopericardium.

Rheumatic fever

This is an important cause of pericarditis, almost invariably associated with severe pancarditis and valvular involvement. Rheumatic pericardial effusion is usually clear, straw-coloured, and sterile. Cardiac tamponade is rare and the fluid usually resorbs rapidly in response to salicylates or steroid therapy. Chronic constrictive pericarditis is never rheumatic in origin, but adherent pericardium with flecks of calcification is not uncommon.

Autoimmune pericarditis

Pericarditis may be the presenting feature of systemic lupus erythematosus, or complicate scleroderma and polyarteritis nodosa. Dry or effusive pericarditis may occur, and it is important to exclude these disorders in patients presenting with idiopathic benign pericarditis. Generally, other signs and symptoms of these collagen vascular diseases will be present.

Granulomatous pericarditis is a complication of rheumatoid arthritis and ankylosing spondylitis, leading to effusion and, occasionally, constriction. Aortitis and aortic insufficiency may be associated, and occasionally there is invasion of the interventricular septum, producing heart block.

Traumatic pericarditis

This produces two forms of pericarditis. One is a direct result of trauma with haemorrhage into the pericardial cavity and formation of haemopericardium. If associated myocardial or valvular injury is absent, complete recovery is the rule, although chronic constriction may develop.

The second type is a form of recurrent pericarditis allied to the postcardiotomy and post-MI syndromes, which may also result in chronic constriction.

Fungal pericarditis

Clinical presentation: Fungal pericarditis occurs as a rare opportunistic infection in immunocompromised patients (e.g. immunosuppressive therapy, HIV/AIDS). It is caused by endemic fungi (*Histoplasma*, *Coccidioides*), non-endemic opportunistic fungi (*Candida*, *Aspergillus*, *Blastomyces*) and semifungi (*Nocardia*, *Actinomyces*).

Diagnosis: Fungal pericarditis may resemble TB pericarditis. Fungal staining and culture of aspirated pericardial fluid and pericardial biopsy are necessary to make the distinction.

Treatment: Antifungal treatment with fluconazole, ketoconazole, itraconazole, amphotericin B or amphotericin B lipid complex is indicated. NSAIDs are used for symptomatic relief. Sulphonamides are the drug of choice for nocardiosis, and a combination of three antibiotics including penicillin should be given for actinomycosis.

Amoebic pericarditis

Pathology: Amoebiasis (caused by *Entamoeba histolytica*) occurs mainly in endemic areas and in travellers from these areas (in whom the syndrome may appear years later). Pericardial complications are rare but when they occur, they carry a high mortality, especially with delayed or missed diagnosis. The usual cause of amoebic pericarditis is extension from an amoebic abscess in the left lobe of the liver. Rarely, spread may also occur from the right lobe, or disease may reach the pericardium from an amoebic lung abscess.

Clinical presentation: There are two modes of presentation: (1) hepatic presentation—an abscess in the proximity of the pericardium, which has not yet ruptured, can cause a pericardial friction rub, a non-purulent pericardial effusion, and ECG and CXR signs of pericarditis; (2) cardiac presentation—perforation of the liver abscess into the pericardium results in a purulent pericarditis. The onset can be acute, with shock and death within a short time, or the onset may be gradual with signs of tamponade as a result of the pericardial fluid.

Diagnosis: Is difficult but should be suspected if, in a patient with a purulent pericarditis and signs of cardiac failure, tenderness of the liver in the epigastrium is much more marked than in the rest of the palpable liver. A high and immobile left hemidiaphragm detected by fluoroscopy or CT scan is also suggestive. Definite diagnosis is by pericardiocentesis (which typically shows brownish fluid; the pus may simulate anchovy sauce) and serological testing for antibodies resulting from invasive amoebiasis (fluorescent antibody test, amoebic enzyme immunoassay, or amoebic gel diffusion test).

Treatment: Hepatic presentation—the pericardial disease resolves with successful treatment of the liver abscess. Cardiac presentation—pericardial drainage and metronidazole. Constrictive pericarditis is an occasional complication.

Constrictive pericarditis vs. restrictive myocardial disease

It is difficult to separate congestive pericarditis from restrictive myocardial disease. The distinction is vital because pericardiectomy is one of the most satisfying operations in terms of cure. Points of differentiation are listed next.

- *Clinical*: murmurs of mitral and tricuspid regurgitation are strong pointers against constrictive pericarditis.
- *ECG*: left axis deviation favours myocardial damage.
- *CXR*: pericardial calcification favours constrictive pericarditis.
- *ECHO*: concentric left ventricular hypertrophy with a 'sparkling granular' appearance in amyloid. Left ventricular hypertrophy may be present in haemochromatosis. Endomyocardial fibrosis is characterized by obliteration of the left ventricular wall. The ejection fraction is normal in constrictive pericarditis, whereas in heart muscle disease, left ventricular function is frequently depressed. On tissue Doppler imaging, a peak early velocity of longitudinal expansion (peak E_a) of ≥ 8.0 cm/s differentiates patients with constriction from those with restriction, with 89% sensitivity and 100% specificity.
- *CT and MRI scan*: these are diagnostic when they show thickened pericardium ≥ 5 mm.
- *Cardiac catheterization*: when the right ventricular and left ventricular end-diastolic pressures differ by more than 6 mmHg, restrictive cardiomyopathy is probably present. A pulmonary artery pressure of more than 50 mmHg strongly favours restrictive cardiomyopathy.
- *Endomyocardial biopsy*: is diagnostic of infiltration in amyloid disease and haemochromatosis. Extensive fibrosis is indicative of restrictive cardiomyopathy.

An exploratory thoracotomy is justified if all these tests fail to make a distinction between the two entities.

Pericardial fluid analysis

Analyses of pericardial effusion can establish the diagnosis of viral, bacterial, tuberculous, fungal, amoebic, and malignant pericarditis. The appearance of the pericardial fluid should be noted. The tests should be ordered according to the clinical presentation of the patient. However, the following routine samples are useful: (1) biochemistry sample for protein and lactate dehydrogenase (LDH) estimation to distinguish between an exudate and a transudate; (2) microbiology specimen for microscopy, culture, and sensitivity testing; (3) cytology specimen. The following tests are requested for diagnosis of the specific forms of pericarditis:

- *viral pericarditis*—PCR for cardiotropic viruses
- *purulent pericarditis*—Gram stain, at least 3 cultures of pericardial fluid for aerobes and anaerobes and blood cultures
- *TB pericarditis*—staining for AFB; bedside inoculation of pericardial fluid into double-strength Kirschner transport medium and culture; ADA level
- *fungal pericarditis*—microscopy and culture
- *amoebic pericarditis*—brownish pericardial fluid with anchovy sauce appearance of pus
- *malignant effusion*—cytology and tumour markers (e.g. CEA).

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The cardiac conduction system

Cardiac action potential

The resting cardiac myocyte is electrically negative, with a transmembrane voltage of between -50 mV and -95 mV. This is due to the distribution of K^+ , Na^+ , Cl^- , and Ca^{2+} ions across the cell membrane. The negativity is maintained by the energy-consuming Na^+/K^+ pump, which transports three Na^+ ions out of the cell for two K^+ ions inward. During phase 4 of the action potential, the voltage slowly increases until a threshold of -60 mV is reached, which opens voltage-gated Na^+ channels and triggers depolarization. The voltage changes in one cell are spread to adjacent cells via gap junctions between them, such that a wavefront of electrical activation is propagated. At least ten distinct ion channels modulate the voltage changes that occur in the action potential (Figs. 10.1 and 10.2).

Automaticity

This is the ability of all cardiac cells to spontaneously depolarize. It is caused by the inward flow of positive ions during diastole. At potentials more negative than -60 mV, ion channels open allowing a slow influx of cations. The slow influx of Ca^{2+} in the sinoatrial node (SAN) allows it to depolarize more rapidly and therefore suppress other potential pacemaker sites.

Sinoatrial node

The SAN sits high in the lateral right atrium (RA) just below the superior vena cava (SVC). It is 1–2 cm in length, 2–3 mm wide, and less than 1 mm from the epicardial surface. It is the dominant site of impulse generation; impulses are conducted out of the sinus node to depolarize the surrounding RA. The SAN is richly innervated with both adrenergic and cholinergic receptors, which alter the rate of depolarization hence controlling the heart rate. Activation spreads out from the SAN to the rest of the RA and left atrium (LA) via specialized interatrial connections including Bachmann's bundle.

Atrioventricular node

The atrioventricular node (AVN) is found in the RA anterior to the mouth of the coronary sinus and directly above the insertion of the septal leaflet of the tricuspid valve. It is the only electrical connection to the ventricle, via the bundle of His, which, like the SAN it is also densely innervated with sympathetic and parasympathetic fibres.

His–Purkinje system

The electrical impulse conducts rapidly through the bundle of His into the upper part of the interventricular septum, where it splits into two branches: the right bundle branch, which continues down the right side of the septum to the apex of the right ventricle and the base of the anterior papillary muscle, and the left bundle branch, which further splits into two fascicles, anterior and posterior. The terminal Purkinje fibres connect with the ends of the bundle branches, forming an interweaving network on the endocardial surface so that a cardiac impulse is transmitted almost simultaneously to the entire right and left ventricles.

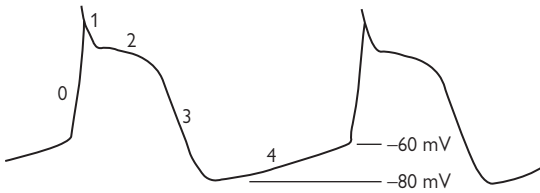


Fig. 10.1 The cardiac action potential.

The action potential has five parts:

0 rapid influx of Na^+ causing fast depolarization

1 rapid early repolarization due to efflux of Na^+

2 plateau phase where repolarization is slowed by an influx of Ca^{2+}

3 repolarization due to the efflux of K^+

4 diastole with a steady-state resting transmembrane voltage.

The plateau phase distinguishes the cardiac from neuronal action potential. The release of Ca^{2+} during phase 2 triggers mechanical contraction of the cell.

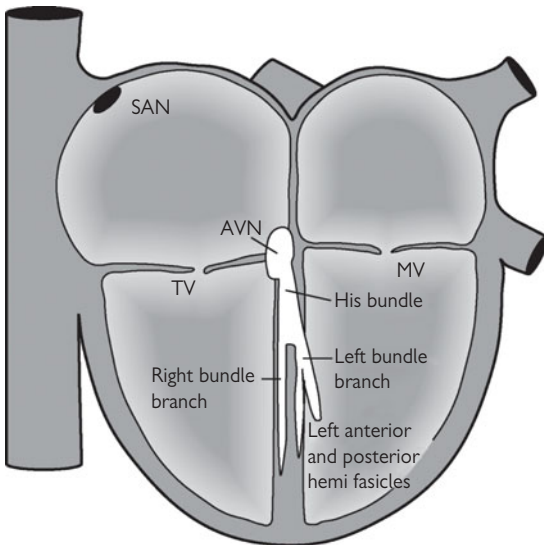


Fig. 10.2 Anatomy of the normal conduction system. AVN = atrioventricular node; MV = mitral valve; SAN = sinoatrial node; TV = tricuspid valve.

Bradycardia: general approach

- Ask specifically about previous cardiac disease, palpitations, blackouts, dizziness, chest pain, symptoms of heart failure, current medication.
- Examine carefully, noting the blood pressure (BP), jugular venous pressure (JVP) waveform (?cannon waves), heart sounds and murmurs, and signs of heart failure.

Investigations

• 12-lead electrocardiogram (ECG) and rhythm strip	Look specifically for the relationship between P waves and QRS complex. A long rhythm strip is sometimes necessary to detect complete heart block if atrial and ventricular rates are similar
• Blood tests	Full blood count (FBC), biochemistry, glucose (urgently) Ca ²⁺ , Mg ²⁺ (especially if on diuretics) Biochemical markers of cardiac injury
• Where appropriate	Blood cultures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) Thyroid function tests (TFTs) Drug levels. Arterial blood gases
• Chest x-ray	Heart size ?Signs of pulmonary oedema

Emergency management


Haemodynamically unstable patients

- Severe haemodynamic compromise (cardiac arrest, asystole, systolic blood pressure (SBP) < 90 mmHg, severe pulmonary oedema, evidence of cerebral hypoperfusion) needs immediate treatment.
- Give oxygen via face mask if the patient is hypoxic on air.
- Keep nil by mouth (NBM) until definitive therapy has been started, to reduce the risk of aspiration in case of cardiac arrest or when the patient lies supine for temporary wire insertion.
- Secure peripheral venous access.
- Give atropine 1 mg IV (MiniJet®) bolus; repeat if necessary up to a maximum 3 mg.
- Give isoprenaline 0.2 mg IV (MiniJet®) if there is a delay in pacing and the patient remains unstable. Set up an infusion (1 mg in 100 mL 1 M saline starting at 1 mL/min titrating to heart rate (HR)).
- Insert temporary pacing wire (technique described in [Temporary ventricular pacing](#), p. 808). If this is not possible immediately, set up an external pacing system and transfer to a screening room for transvenous pacing.
- Look for and treat reversible causes; drug overdose (β -blockers, verapamil, diltiazem, digoxin), hypothyroidism, hypothermia, myocardial infarction (MI), infective endocarditis).

Haemodynamically stable patients

- Admit to the coronary care unit (CCU) with continuous ECG monitoring.
- Keep atropine drawn up and ready in case of acute deterioration.
- Avoid temporary pacing wire unless there is haemodynamic deterioration.

Long-term management

- Ensure all possible *underlying causes* have been identified and removed.
- Regardless of aetiology if symptomatic bradycardia remains refer for *permanent pacing* (see  p. 530).
- Complete heart block should always be referred for a permanent pacemaker, whether symptomatic or not.

External cardiac pacing

- In emergencies, external cardiac pacing (via an external defibrillator that can pace) may be used first, but this is only a temporary measure until a more 'definitive' transvenous pacing wire can be inserted.
- The defibrillator ECG electrodes need to be attached.
- Attach the defibrillation patches to the anterior and posterior chest wall. Turn the output up (in volts or amperes) until ventricular capture with QRS complexes is seen. This will also cause extremely unpleasant thoracic muscular capture, so the patient must be sedated with benzodiazepam.
- External cardiac pacing is useful as a standby in patients, e.g. post-MI, when the risks of prophylactic transvenous pacing after thrombolysis are high.
- Haemodynamically stable patients with anterior MI and bifascicular block may be managed simply by application of the external pacing electrodes and having the pulse generator ready if necessary.
- Familiarize yourself with the machine in your hospital when you have some time—a cardiac arrest is not the time to read the manual for the apparatus!

Sinus bradycardia

In sinus bradycardia, the SAN discharges $<60/\text{min}$. P waves are normal but slow. It may be normal (e.g. in sleep, healthy resting hearts).

Causes

- Young athletic individual
- Healthy resting heart, e.g. sleep
- Chronic degeneration of sinus or AV nodes or atria
- Drugs— β -blockers, morphine, amiodarone, calcium-channel blockers, lithium, propafenone, clonidine
- Increased vagal tone
 - vasovagal attack
 - nausea or vomiting
 - carotid sinus hypersensitivity
- Hypothyroidism
- Hypothermia
- MI or ischaemia of the sinus node
- Cholestatic jaundice
- Raised intracranial pressure

Sinus pause

The SAN fails to generate impulses (sinus arrest) or the impulses are not conducted to the atria (SA exit block). A single dropped P wave with a PP interval that is a multiple of the basic PP interval suggests exit block. A period of absent P waves suggests sinus arrest. Causes include, excess vagal tone, acute myocarditis, MI, aging (fibrosis), stroke, digoxin toxicity, and anti-arrhythmic drugs.

Sick sinus syndrome

This syndrome encompasses a number of conduction system problems: persistent sinus bradycardia not caused by drugs, sinus pauses, AV conduction disturbances, and paroxysms of atrial arrhythmias. It is usually diagnosed by ambulatory cardiac monitoring.

Atrioventricular block

This can occur at the AVN (nodal) or His–Purkinje system (infranodal). Common causes are ischaemic heart disease (IHD), conduction system fibrosis (aging), calcific aortic stenosis, congenital, cardiomyopathy, hypothermia, hypothyroidism, trauma, radiotherapy, infection, connective tissue disease, sarcoidosis, and anti-arrhythmic drugs. AV block is further classified:

First-degree AV block

Every impulse conducts to the ventricle but the conduction time is prolonged. Every P wave is followed by a QRS but with a prolonged PR interval (>200 ms). If the QRS width is normal then the block is at the AV node, if the QRS shows aberration (right (RBBB) or left bundle branch block (LBBB)), then the block may be at the AV node or the His–Purkinje system.

Second-degree AV block

- *Mobitz 1* (Wenckebach): ECG shows the PR interval prolongs until a P wave is not conducted. The PR interval following the dropped P wave must be the shortest. The RR interval is therefore irregular. This block is characteristic of the AVN.
- *Mobitz 2*: ECG shows a fixed P to QRS ratio of 2:1, 3:1, or 4:1. Block is predominantly at the His bundle and there is often an aberrant pattern to the QRS complex.

Third-degree AV block (complete heart block)

There is no conduction to the ventricle. The ECG shows dissociation between the P and QRS complexes. An escape pacemaker rhythm takes over. A narrow QRS indicates AVN block, and the His bundle is the pacemaker, which is faster and more stable than more distal sites. A wide QRS indicates infranodal block and a distal ventricular pacemaker site. Asystole may occur; therefore, this carries a worse prognosis. This type of heart block always requires implantation of a permanent pacemaker.

Causes of atrioventricular block

- Conduction system fibrosis (aging)
- Associated with acute myocardial infarction or ischaemia
- Drugs (β -blockers, digitalis, Ca^{2+} -channel blockers)
- Increased vagal tone
- Trauma or following cardiac surgery/catheter ablation
- Calcific aortic stenosis
- Infective endocarditis
- Hypothyroidism
- Hypothermia
- Myocarditis (diphtheria, rheumatic fever, viral, Chagas' disease)
- Associated with neuromuscular disease, i.e. myotonic dystrophy.
- Collagen vascular disease (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma)
- Cardiomyopathies (haemochromatosis, amyloidosis)
- Granulomatous disease (sarcoid)
- Congenital heart block
- Congenital heart disease (atrial septal defect (ASD), Ebstein's, patent ductus arteriosus (PDA)).

Bundle branch block

This is due to disease in the His–Purkinje system causing a QRS > 120 ms. Common causes are conduction system fibrosis (aging), IHD, hypertension, cardiomyopathies, cardiac surgery, infiltrative diseases (e.g. amyloid).

- **LBBB** (Fig. 10.3): LV depolarization is delayed, giving a wide QRS, large notched R waves in leads I and V₆, and a deep S wave (may be preceded by small R wave) in V₁. Block confined to the anterior or posterior fascicles of the left bundle gives left-axis or right-axis deviation respectively on the ECG. BBB leads to asynchronous contraction of the left and right ventricle, which reduces cardiac output, important in heart failure.
- **RBBB**: RV depolarization is delayed, giving wide QRS, an RSR pattern in V₁, and a slurred S wave in I and V₆. This can be a normal variant but more commonly as a result of causes listed above and, in addition, ASD, pulmonary embolism (PE), cor pulmonale.
- **Bifascicular block** (Fig. 10.4) = RBBB + left anterior hemiblock (left-axis deviation on ECG), RBBB + left posterior hemiblock (right-axis deviation on ECG), or LBBB. All of these may progress to complete AV block.
- **Trifascicular block** = bifascicular block + 1st-degree AV block.

Management

- Conventional teaching is that LBBB is always pathological, and thorough investigation for an underlying cause is needed (echocardiogram, cardiac MR, coronary angiography); however, a cause may not be found. RBBB may occur in otherwise completely normal hearts.
- Permanent pacing is not normally needed for isolated RBBB or LBBB, unless associated with more advanced levels of block (bi- or trifascicular block), symptomatic bradycardia, syncope.

Common causes of bundle branch block

- IHD
- Hypertensive heart disease
- Valve disease (especially aortic stenosis)
- Conduction system fibrosis (aging)
- Myocarditis or endocarditis
- Cardiomyopathies
- Pulmonary hypertension
- Trauma or post-cardiac surgery
- Neuromuscular disorders (myotonic dystrophy)
- Polymyositis.

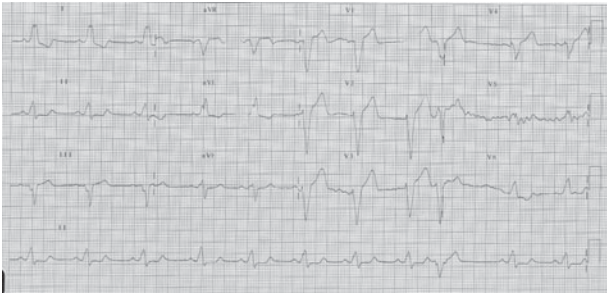


Fig. 10.3 ECG showing LBBB. There is a wide QRS complex with large notched R waves in leads I and V₆ and a deep S wave in V₁.



Fig. 10.4 ECG showing bifascicular block. There is a wide QRS complex with an rSr pattern in V₁ and deep slurred S wave in V₆ (=RBBB). The QRS in lead 1 is positive and lead aVF negative (=left anterior hemiblock). There is also 2nd-degree AV nodal block (Mobitz type 1 or Wenkebach). Observing the rhythm strip from the first P wave, there is a gradually prolonging PR interval and the P wave that follows the 6th QRS complex is blocked.

Tachycardia: general approach

Tachyarrhythmias may present with significant symptoms and haemodynamic compromise. The approach to patients depends upon the following factors:

The effect of the rhythm on the patient

- *Patients with cardiac arrest*—immediate unsynchronized DC shock (follow advanced life support (ALS) guidelines)
- *Patients with signs of severe haemodynamic compromise*:
 - shock; low BP, cool peripheries, sweating
 - cerebral hypoperfusion; confusion, agitated, depressed conscious level
 - pulmonary oedema
 - chest pain

Record an ECG/rhythm strip and treat immediately with synchronized DC shock

- *Patients without haemodynamic compromise*: record an ECG and diagnose tachyarrhythmia. Follow the treatment algorithm outlined here. If they deteriorate, treat as above.

Diagnosing the arrhythmia

The main distinctions to make are:

- tachy- (>120/min) vs. brady- (<60/min) arrhythmia
- narrow (≤ 120 ms or 3 small squares) vs. broad QRS complex
- regular vs. irregular rhythm.

Investigations for patients with tachyarrhythmias

12-lead ECG and rhythm strip	<ul style="list-style-type: none"> ● Regular vs. irregular rhythm ● Narrow vs. broad QRS complex
Blood tests	<ul style="list-style-type: none"> ● FBC, biochemistry, glucose (urgently) ● Ca^{2+}, Mg^{2+} (especially if on diuretics) ● Biochemical markers of myocardial injury
Where appropriate	<ul style="list-style-type: none"> ● Blood cultures, CRP, ESR ● Thyroid function tests ● Drug levels ● Arterial blood gases
Chest X-ray (CXR)	<ul style="list-style-type: none"> ● Heart size ● Evidence of pulmonary oedema ● Other pathology (e.g. Ca^{2+} bronchus \rightarrow AF, pericardial effusion \rightarrow sinus tachycardia, hypotension \pm AF)

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Tachycardia: emergency management

History

Previous cardiac disease, palpitations, dizziness, chest pain, symptoms of heart failure and recent medication. Ask specifically about conditions known to be associated with certain cardiac arrhythmias (e.g. AF—alcohol, thyrotoxicosis, mitral valve disease, IHD, pericarditis; VT—previous MI, LV aneurysm).

Examination

BP, heart sounds and murmurs, signs of heart failure, carotid bruits.


Management (Fig. 10.5)


Haemodynamically unstable patients

Tachyarrhythmias causing severe haemodynamic compromise require urgent correction, usually with external defibrillation. Drug therapy requires time and haemodynamic stability.

- The only exception is a patient in chronic AF with an uncontrolled ventricular rate—defibrillation is unlikely to cardiovert to sinus rhythm (SR). Rate control and treatment of precipitant is first-line.
- Sedate awake patients with midazolam (2.5–10 mg IV) ± diamorphine (2.5–5 mg IV + metoclopramide 10 mg IV) for analgesia. Beware respiratory depression and have flumazenil and naloxone to hand.
- Formal anaesthesia with propofol is preferred, but remember the patient may not have an empty stomach and precautions should be taken to prevent aspiration (e.g. cricoid pressure, endotracheal (ET) intubation).
- Start at 200 J synchronized shock and increase as required.
- If tachyarrhythmia recurs or is unresponsive try to correct $\downarrow P_aO_2$ (partial pressure of oxygen in the arterial blood), $\uparrow P_aCO_2$ (partial pressure of carbon dioxide in the arterial blood), acidosis or $\downarrow K^+$. Give Mg^{2+} (8 mmol IV stat) and shock again. Amiodarone 150–300 mg bolus IV may also be used.
- If there is ongoing ventricular tachycardia (VT) in the context of cardiac arrest or recurrent VT episodes, causing haemodynamic compromise, requiring repeated DC cardioversions then give IV amiodarone (300 mg IV bolus, followed by 1.2 g IV over 24 hours via central venous line). Follow Resuscitation Council periarrest arrhythmia guidelines.¹

Haemodynamically stable patients

- Admit and arrange for continuous ECG monitoring and 12-lead ECG.
- Try vagotonic manoeuvres (e.g. Valsalva/carotid sinus massage).
- If diagnosis is clear, introduce appropriate treatment.
- If there is doubt regarding diagnosis, give adenosine 6 mg as a fast IV bolus followed by 5 mL saline flush. If there is no response, try 9, 12, and 18 mg in succession with continuous ECG rhythm strip.
- Definitive treatment should start as soon as diagnosis is known (see  Treatment options in tachyarrhythmias, p. 721).
- First episodes of atrioventricular node re-entrant tachycardia (AVNRT), atrioventricular re-entrant tachycardia (AVRT), or focal atrial tachycardia may need no further treatment. All other diagnoses and Wolff–Parkinson–White syndrome (WPW) should be referred to a cardiologist for further investigation and management.

¹ Resuscitation Council (UK) guidelines  www.resus.org.uk.

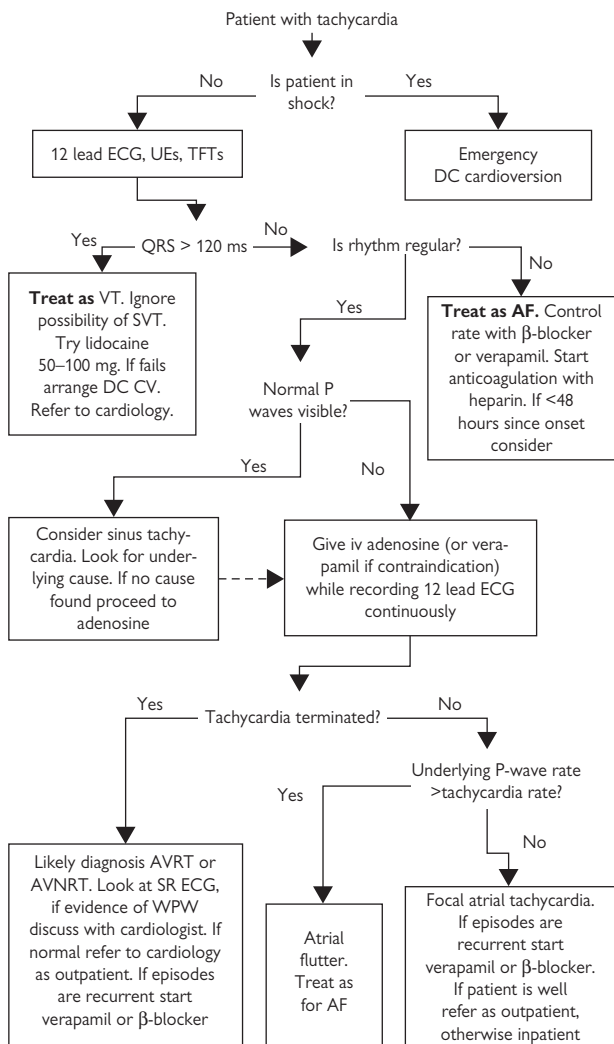


Fig. 10.5 Guidelines to the safe management of arrhythmias in the emergency department (adapted from Barts and the London NHS Trust A+E guidelines). CV = cardioversion; UEs = urea and electrolytes.

Tachyarrhythmias: classification

Fast heart rates can be classified in various ways; however, an anatomical approach should be used, which can then be subdivided mechanistically. This provides a simple foundation for understanding the ECG appearance and the tachycardia mechanism.

Atrial tachyarrhythmias

These are contained completely in the atria (or SAN) and are characterized by:

- sinus tachycardia
- sinus node re-entrant tachycardia (SNRT)
- atrial fibrillation (AF)
- atrial tachycardia
 - focal atrial tachycardia
 - macro-re-entrant atrial tachycardia (=atrial flutter).

Atrioventricular tachyarrhythmias

These are dependent on activation between the atrium and ventricle (or AV node). They are characterized by:

- AVRT
- AVNRT
- junctional tachycardia.

Ventricular tachyarrhythmias

These are contained completely in the ventricle and are characterized by:

- VT
 - monomorphic VT.
 - polymorphic VT (torsades de pointes).
- ventricular fibrillation (VF).

Features of a broad complex tachycardia suggesting ventricular origin

- AV dissociation (NB: VA conduction may be present during VT).
 - independent P waves.
 - capture and fusion beats
- QRS width >140 ms (if RBBB appearance) or >160 ms (if LBBB appearance)
- QRS axis <-30 or $>+90$.
- Concordance of QRS complexes in precordial leads (all positive or all negative)
- Absence of RS or RS >100 ms in precordial leads

Supraventricular causes of a broad complex tachycardia

- SVT + aberrancy (bundle branch block)
- SVT + pre-excitation (activation of the ventricle over a pathway other than the AV node)
- Antidromic AVRT
- SVT + class 1c drug (flecainide).

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ECG diagnosis of tachyarrhythmias

By following simple rules when interpreting the ECG, any tachycardia can be classified to the categories described earlier; however, the ECG should always be considered in the clinical context. A broad complex tachycardia (BCT) must *always* be diagnosed as VT in the acute setting, as treating such patients incorrectly may be fatal. View the ECG in both tachycardia and the patients' usual rhythm to make a diagnosis (e.g. may see features of WPW). For narrow complex tachycardias (NCTs), use carotid sinus massage or adenosine boluses to see the underlying atrial rhythm.

A simple approach follows (Fig. 10.6):

1. Is the tachycardia regular?

Grossly irregular RR intervals regardless of other ECG features indicate AF (or VF; however expect the patient to be unconscious!). A slight irregularity can occur in other tachycardias, particularly at their onset. Alternatively, multiple atrial and/or ventricular ectopic beats or atrial tachycardia with variable AV block can give irregularity.

2. Is the QRS complex broad (>120 ms)?

Yes—ventricular in origin, no—supraventricular.

SVT should only be considered for a BCT when there is strong clinical suspicion (e.g. young patient, no previous cardiac history, normal RV and LV function, no accompanying cardiovascular compromise) and after discussion with senior colleagues. NB: Look at the SR ECG (if available) for pre-existing bundle branch block or pre-excitation (suggesting an accessory pathway).

3. Identify P waves, their morphology and P:R ratio

- 1:1 P:R, normal P-wave morphology: sinus tachycardia, focal atrial tachycardia originating from close to the SA node (high crista terminalis or right superior pulmonary vein) or, rarely, SNRT.
- 1:1 P:R, abnormal P-wave morphology: focal atrial tachycardia. AVRT or AVNRT (if slow activation from ventricle to atrium = long RP tachycardia).
- P waves not visible: AVRT or AVNRT (with fast activation from ventricle to atrium). Compare QRS morphology in tachycardia with SR, as a slight deflection in the tachycardia QRS complex not seen in SR may represent the P wave.
- P:R 2:1,3:1 or greater: focal or macro-re-entrant atrial tachycardia with AV nodal block.
- P-wave rate >250/min: this defines atrial flutter (macro-re-entrant atrial tachycardia). Usually there will be 2:1 or 3:1 P:R ratio. In typical atrial flutter, a characteristic saw-tooth baseline is seen in the inferior leads.

4. Response to AV block (adenosine or carotid massage)

If a rapid P-wave rate persists despite induced AV nodal block, then the tachycardia is independent of the AV node, i.e. macro-re-entrant or focal atrial tachycardia and SNRT. If tachycardia is terminated by AV nodal block, it is either AVRT or AVNRT (rarely, junctional tachycardia). Focal atrial tachycardia and SNRT may also be terminated by adenosine, not due to AV nodal block, but because they are adenosine sensitive.

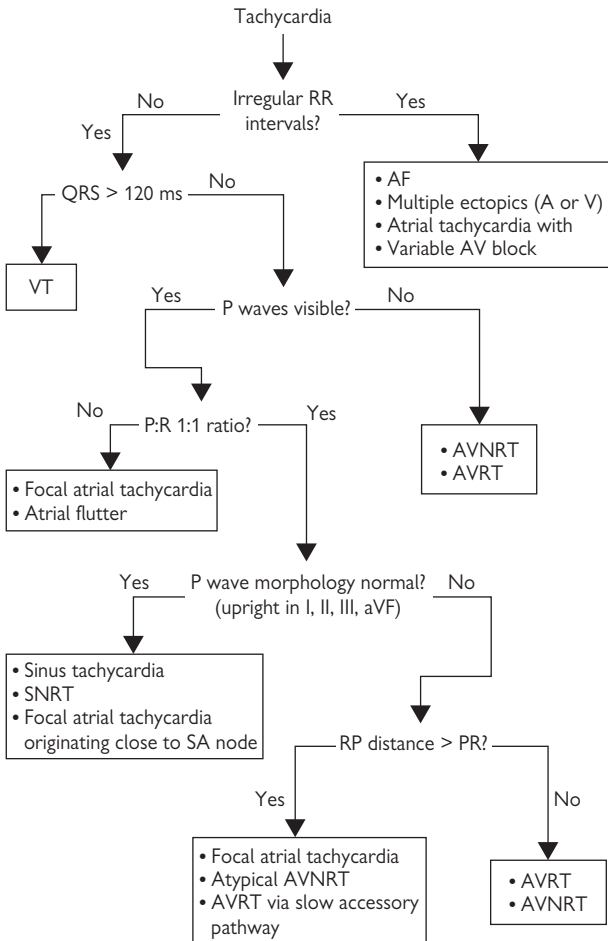


Fig. 10.6 ECG diagnosis of tachycardia.

Supraventricular tachycardia (see Fig. 10.7)

This section deals with the diagnosis and pharmacological management of individual SVTs. Their mechanisms and ablation are discussed in detail in Chapter 11.

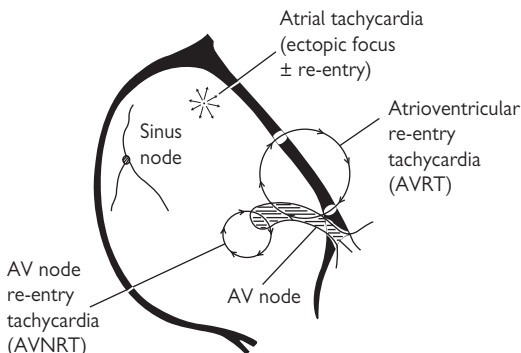


Fig. 10.7 Types of supraventricular tachycardia. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd ed. Oxford: Oxford University Press.




Sinus tachycardia

Defined as a sinus rate $>100/\text{min}$, this may be physiological (e.g. exercise or emotion) or pathological. Look for and treat the underlying cause—anaemia, drug related (e.g. caffeine, cocaine, salbutamol, etc.) hyperthyroidism, pain, hypoxia, pyrexia, or hypovolaemia. If no underlying cause is found, consider SNRT or focal atrial tachycardia as alternative diagnoses. These will be paroxysmal in nature, have sudden onset or offset and are usually terminated by IV adenosine. If no underlying cause is found, it may be termed *inappropriate sinus tachycardia*. β -blockers are useful for symptomatic persistent inappropriate sinus tachycardia, and vital in controlling the sinus rate in hyperthyroidism or heart failure, or post MI.


Sinus nodal re-entrant tachycardia

This is a rare cause of narrow complex tachycardia due to a micro re-entry circuit within the SAN. ECG is identical to sinus tachycardia, making diagnosis difficult. β -blockers or calcium-channel antagonists are the first-line treatment. Modification of the SA node by radiofrequency ablation (RFA) is reserved for drug-refractory cases or those not wishing to take drugs.

Regular tachycardia

- Sinus tachycardia
- SNRT
- Atrial tachycardia (see  Atrial tachycardia, p. 496).
 - focal atrial tachycardia
 - macro-re-entrant atrial tachycardia (atrial flutter).
- AVRT (i.e. with accessory path, e.g. WPW) (see  Atrioventricular re-entrant tachycardia (AVRT), p. 498)
- AVNRT (see  Atrioventricular nodal re-entrant tachycardia (AVNRT), p. 498)

Irregular tachycardia

- Atrial fibrillation (see  Atrial fibrillation, p. 500)
- Atrial flutter with variable AV block
- SR with frequent atrial or ventricular ectopic beats

Atrial tachycardia


The term atrial tachycardia describes all regular atrial rhythms with a P rate >100/min, regardless of the mechanism, and this should be prefixed by either focal or macro-re-entrant, unless the mechanism is unknown.

Focal atrial tachycardia

This is due to an automatic focus of atrial cells firing faster than the SA node. The P-wave morphology and axis during tachycardia can be used to predict the location of the source. They are characteristically paroxysmal with short bursts at a rate of 150–250/min, but may be incessant, risking tachycardia-induced cardiomyopathy. They occur in normal hearts but are also associated with many forms of cardiac disease. It may be terminated with IV adenosine.

Treatment is needed only for symptomatic patients or incessant tachycardia. β -blockers and calcium-channel antagonists can be used to slow the atrial rate and the ventricular response by AV nodal blockade. Class 1c (flecainide and propafenone) or class 3 (amiodarone and sotalol) may suppress the tachycardia, but their use is limited by toxicity. RFA is the most effective therapy and is a cure.

Macro-re-entrant atrial tachycardia (atrial flutter)

Atrial flutter (AFL) is an ECG definition of a P-wave rate >240/min, and an absence of an isoelectric baseline between deflections. It is caused by a re-entry circuit over large areas of the right or left atrium (see  Atrial arrhythmias: mechanism, p. 564). The circuit is not influenced by adenosine, and the AVN block reveals the underlying rhythm. It is usually (but not always) associated with structural heart disease. AFL exacerbates heart failure symptoms and, if incessant, will worsen LV function.

DC cardioversion effectively restores SR, but AFL often recurs. Drug therapy is not very effective. AVN blockade is difficult to achieve and the high doses of β -blockers, calcium-channels antagonists, and digoxin required may have unwanted side-effects. Class 1c drugs are used to maintain SR; however, propafenone and flecainide can paradoxically accelerate the ventricular rate in AFL by slowing the tachycardia rate down sufficiently to allow the AVN to conduct 1:1. They should always be used in combination with an AVN-blocking agent. Amiodarone is an alternative agent, particularly if LV function is impaired.

RFA is the most effective way of maintaining SR and is a cure. If curative ablation is not possible, and effective rate control is not possible with drugs, then ablation of the AV node and a pacemaker is a permanent palliative solution. Anticoagulation recommendations for patients with AFL are identical to those for patients with AF.¹

¹ Blomstrom-Lundqvist C, Scheinman MM, Aliot EM et al. (2003). ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias *J Am Coll Cardiol* **42**: 1493–531.

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Atrioventricular nodal re-entrant tachycardia (AVNRT) (see Figs. 10.8 and 10.9)

This is the commonest cause of a narrow complex tachycardia in patients with normal hearts, typically in young adults, commoner in women. It characteristically causes paroxysms of severe palpitations, with a pounding in the neck (due to reflux of blood into the jugular veins caused by the simultaneous atrial and ventricular contraction). It has a benign prognosis and may require no treatment. The ECG in SR is usually normal.

The tachycardia is terminated by IV adenosine or vagal manoeuvres. The underlying re-entry circuit is entirely within the AV node and therefore can be controlled long term with β -blockers, verapamil, or diltiazem. Alternative effective, but second-line agents are flecainide, propafenone, or sotalol. The first-line treatment for recurrent symptomatic episodes however is RFA, which is a cure. When symptoms are very infrequent, a 'pill in the pocket' approach is sometimes helpful, i.e. a large oral dose of, e.g., verapamil is taken to terminate the event.

Atrioventricular re-entrant tachycardia (AVRT) (see Figs. 10.8 and 10.9)

This is due to an AV re-entry circuit involving a connection other than the AV node. As these accessory pathways are congenital, arrhythmias usually present much younger than AVNRT (infancy or childhood). Rapid paroxysmal palpitations are the usual symptom. It is usually a NCT (orthodromic), as the ventricle is activated via the AVN; however, a BCT is also possible if the ventricle activates via the accessory pathway (antidromic). The prognosis may not be benign and specialist referral is mandatory. RFA is the treatment of choice. The most useful drugs are flecainide and propafenone, which slow conduction in the accessory pathway without slowing the AV node. Verapamil, diltiazem, and digoxin should be avoided only when ventricular pre-excitation is present.

Junctional tachycardia

This term should only be used for focal tachycardias that originate from the AV nodal tissue directly, and are in fact rare in adult cardiology. Distinction from other forms of NCT is only possible at the electrophysiology (EP) study. RFA is high risk as the AV may be damaged. β -blockers and flecainide are effective.

Further reading

Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. (2003). ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias. *J Am Coll Cardiol* **42**: 1493–531.

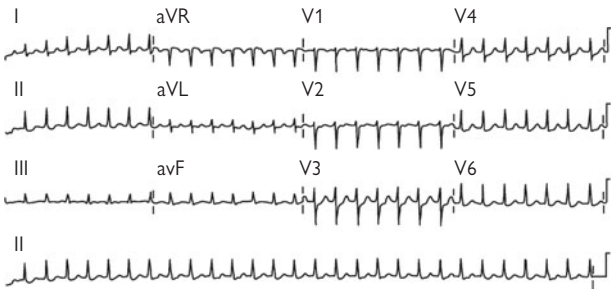


Fig. 10.8 Typical presenting ECG of AVNRT or AVRT. A narrow complex tachycardia without visible P waves.

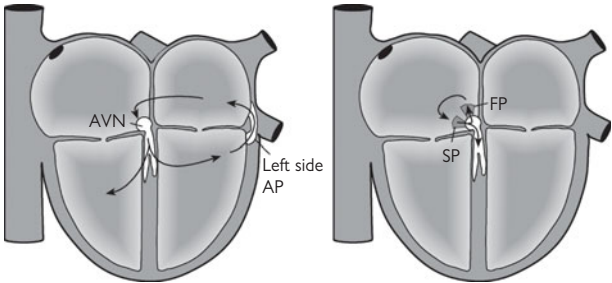


Fig. 10.9 Mechanism of AVNRT and AVRT. Both AVNRT and AVRT have re-entry mechanisms. Orthodromic AVRT via a left-sided accessory pathway (AP) (left). Activation from A to V is down the atrioventricular node (AVN), then across the ventricular myocardium and back from V to A up the AP, thus completing the circuit. The ventricle therefore is an essential part of the circuit. Antidromic AVRT (not shown) would activate in the opposite direction. Typical AVNRT (right) activates from the atrium to the AVN via the slow pathway (SP) and from the AVN to the atrium via the fast pathway (FP), thus completing the circuit. The ventricle is activated as a bystander via the bundle of His and is not an essential part of the circuit. Atypical AVNRT (not shown) activates in the opposite direction.

Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 0.5–1% in the general population but 10-fold greater in those aged over 65 years. It is an atrial arrhythmia where uniform activation is replaced by chaos, such that co-ordinated contractile function is lost and the atria dilate. It is characterized by an ECG lacking any consistent P waves, and a rapid, irregular ventricular rate.

Classification

Previously, many terms have been used to prefix AF; however, an international consensus on nomenclature has now been reached.¹ This allows the correct selection of management options for patients. All episodes of AF lasting greater than 30 s should be described as:

- *first detected* or a *recurrent episode*
- *self-terminating* or *not self-terminating*
- *symptomatic* or *asymptomatic*.
- *paroxysmal* (if self-terminating within 7 days)
- *persistent* (if cardioverted to SR by any means or lasts >7 days regardless of how it terminates)
- *permanent* (if cardioversion to SR is not possible or is not undertaken)
- *lone* (in the absence of underlying structural heart disease), or *idiopathic* (in the absence of any disease).

Causes AF is a common end-point for many forms of cardiac disease where atrial myocytes are damaged or subject to adverse stress generated by ischaemia, cyanosis, or elevated intracavity or pericardial pressures. These changes alter the conduction properties of the myocardium, facilitating fibrillation (see Table 10.1).

Table 10.1 Causes of atrial fibrillation

Common causes	Potentially reversible causes	Rare causes
<ul style="list-style-type: none"> ● Hypertension ● Left ventricular (LV) failure (any cause) ● Coronary artery disease (CAD) ● Mitral or tricuspid valve disease ● Hypertrophic obstructive cardiomyopathy (HOCM) 	<ul style="list-style-type: none"> ● Alcohol binge ● Pneumonia ● Hyperthyroidism ● Acute MI ● Acute pericarditis ● Myocarditis ● Exacerbation of pulmonary disease ● Pulmonary embolism ● Cardiac surgery 	<ul style="list-style-type: none"> ● Congenital heart disease ● Autonomic 'vagal' overactivity ● Pericardial effusion ● Cardiac metastases ● Myocardial infiltrative diseases (e.g. amyloid) ● Atrial myxoma

¹ Levy S, Camm AJ, Saksena S, et al. (2003). International consensus on nomenclature and classification of atrial fibrillation. *J Cardiovasc Electrophysiol* **14**: 443–5.

Symptoms and signs

Palpitations, dyspnoea, fatigue, presyncope, syncope, and chest pain are common; however, 30% of patients present with AF as an incidental finding only. Ambulatory monitoring reveals that even patients with symptomatic paroxysmal AF have many asymptomatic episodes. Physical findings are an irregular pulse (which if rapid will be faster at the apex than the wrist), variable intensity of the first heart sound, and absent 'a' waves in the JVP.

Atrial fibrillation: investigations

A reversible cause should be identified early to allow appropriate treatment. The most important investigations are:¹

- **ECG:** irregular ventricular rate and absence of P waves. V rate depends on intact AV nodal function. In the presence of complete AV nodal block, a slow regular ventricular escape rhythm is present. The QRS will be broad if there is aberrant conduction; ST–T-wave changes may be due to rapid rate, digoxin, or underlying cardiac disease.
- **ECHO±transoesophageal echocardiography (TOE):** for LV function, valve lesions, pericardial effusion, and to exclude intracardiac thrombus prior to version to SR. LA size is an important predictor of likely future maintenance of SR.
- **thyroid function:** thyrotoxicosis may present as AF only.
- **CXR:** cardiomegaly, pulmonary oedema, intrathoracic precipitant, valve calcification (mitral stenosis (MS)).
- **urea and electrolytes (U&Es):** hypokalaemia, renal impairment.
- **troponin or cardiac enzymes:** ?MI. Expect small rise after DC shock. Troponin may be elevated with any prolonged tachycardia without an acute coronary syndrome.
- **drug levels:** especially if taking digoxin.
- **arterial blood gases (ABGs):** if hypoxic, shocked or ?acidotic.
- **other investigations** depend on suspected precipitant.

Other investigations when the patient is stable

24-hour ambulatory monitor to assess heart-rate control and look for episodes of symptomatic bradycardia, exercise test (or other ischaemia stress test), coronary angiography, cardiac magnetic resonance.

1 Wyse DG, Waldo AL, DiMarco JP et al. (2002). A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* **347**: 1825–33.

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Atrial fibrillation: management (see Fig 10.10)

The most important aspects of AF management are preventing stroke and controlling patients' symptoms, *not* restoration of SR. Limiting the ventricular rate by pharmacologically blocking the atrioventricular (AV) node (*rate control*) is safe and often effective. Currently available antiarrhythmic drugs (AADs) that maintain SR (*rhythm control*) are limited by their toxicity and efficacy, which explains why a strategy of rhythm control (electrical cardioversion and AADs) may be worse than rate control alone.¹ Non-pharmacological strategies (ablation) and new effective, safer AADs for rhythm control may change this paradigm in the future. Fig. 10.10 summarizes contemporary AF management.

Emergency management

If the patient is haemodynamically compromised, then urgent external DC cardioversion under general anaesthesia or sedation is needed. This is rarely necessary, and rate control is usually sufficient to control symptoms. If symptoms persist despite rate control, cardioversion can be attempted pharmacologically with flecainide (2 mg/kg, max 150 mg, infused via a peripheral line over 30 min) or if LV impairment is suspected, amiodarone (5 mg/kg, max 300 mg infused via a central line). Patients must be monitored throughout for possible ventricular arrhythmia and hypotension. If AF has been present for >48 hours, cardioversion should be preceded by a TOE to exclude atrial thrombus. All patients should be warfarinized for at least 4 weeks post cardioversion.

Rate control

Drugs: The first-line agents are β -blockers or non-dihydropyridine calcium-channel antagonists (verapamil or diltiazem), which are effective during both exercise and rest. Digoxin is effective at rest only, and should be considered a second-line agent. Rate control can be assessed by a 24-hour Holter monitor ensuring heart rates; at rest these are <80 bpm, mean <100 bpm, during moderate exercise <120 bpm.

Pace and ablate: See below.


Rhythm control

If symptoms are not improved by rate control alone, or a reversible cause of AF has been treated, then rhythm control should be attempted. The trials of rate vs. rhythm control under-represent younger patients (<65 years old), so in this group an aggressive strategy of rhythm control may be warranted regardless of symptoms. For persistent AF, SR is *restored* by DC cardioversion. AADs or non-pharmacological methods are usually needed to *maintain* sinus rhythm.

Drugs: Flecainide, propafenone, sotalol, disopyramide, and quinidine are all more effective than placebo in maintaining SR. They all can lead to long QT-related VT/VF and are contraindicated in patients with structural heart disease. Amiodarone is the most effective drug; however, its use is limited by non-cardiac side-effects, and it is not tolerated by up to 25%. If AV nodal

¹ NICE 2006 guidelines for anticoagulation in AF.

function and QT interval are normal, these drugs can safely be started out of hospital. QRS width and QT interval should be monitored on a weekly basis until a target maintenance dose is reached.

Catheter and surgical ablation: This is the most effective method of maintaining SR but carries a small procedural risk (see  Catheter ablation of atrial fibrillation, p. 568).

Pacemakers: Various pacemaker strategies are useful in maintaining SR. Atrial pacing modes (AAI or DDD) are mandatory, as they reduce the AF burden.

- 'Vagal AF' is prevented by pacing.
- SAN disease symptoms are improved by a 'block and pace' regimen, i.e. rate-controlling drugs for AF and pacing for bradycardic episodes.
- Algorithms to suppress atrial ectopy, or multisite atrial pacing, are not very effective strategies to prevent AF.
- *Pace and ablate:* this is a palliative strategy when symptoms continue because adequate rate or rhythm control is not possible with drugs or by other means such as ablation. A pacemaker is implanted, and 6 weeks following this, iatrogenic irreversible complete heart block is induced with radiofrequency ablation. This can bring dramatic symptom improvement; however, patients are rendered pacing dependent.

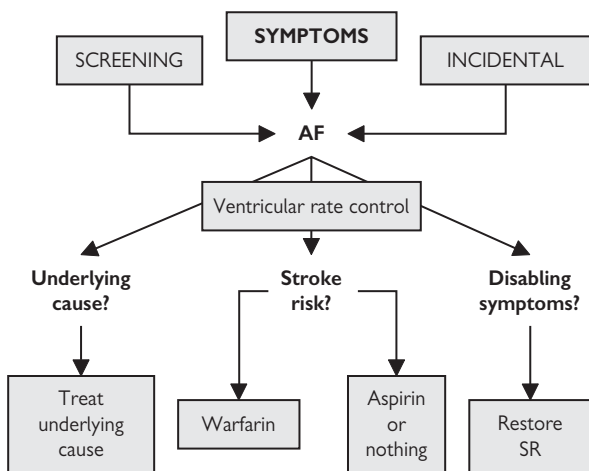


Fig. 10.10 Contemporary management of atrial fibrillation.

Anticoagulation

Warfarin (international normalized ratio (INR) >2) reduces strokes in AF by 60%, regardless of underlying risk, and is the current standard by which other anticoagulation strategies are judged. Unfortunately, not all eligible patients receive it. Problems are that it can be subtherapeutic (INR too low) or cause bleeding complications (INR too high). Decisions on whether to use warfarin long term depend on the patients' overall stroke risk, and no distinction should be made between paroxysmal, persistent, or permanent AF. The CHADS₂ (Congestive heart failure, Hypertension, Age >75 , Diabetes mellitus, and previous Stroke; see Table 10.2) score is a very simple stroke risk calculator (warfarin needed if score ≥ 2). More complex guidelines are available from the National Institute for Health and Clinical Excellence (NICE).¹ Therapeutic anticoagulation with warfarin is always needed for at least 4 weeks pre- (unless TOE performed) and 4 weeks post-cardioversion.

Aspirin (75–300 mg) has been shown in a meta-analysis to reduce strokes in AF by 20%; however, it is not clear whether this benefit is due to its effects on vascular disease rather than thrombogenesis per se. It is inferior to warfarin.

Aspirin + clopidogrel (75 mg + 75 mg) has a lower annual stroke rate than aspirin alone (2.4% vs. 3.2%), but is not as effective as warfarin, even though it carries the same risk of bleeding complications. It should not be considered an equivalent alternative to warfarin.

New pharmacological agents: Direct thrombin inhibitors are currently under evaluation but not yet licensed. Dabigatran 150 mg bd has been shown to be more effective than warfarin, with the same incidence of bleeding complications. At 110 mg bd, it is equivalent to warfarin with less bleeding. Monitoring of INR is not needed. Likely problems are compliance (needs to be taken twice daily), reversal of anticoagulation in emergency, and cost.

Left atrial appendage occlusion: Most strokes in AF are due to thrombus emerging from the LA appendage. A custom-made Nitinol mesh (Watchman[®]) can be delivered percutaneously via the femoral vein and a trans-septal puncture to the appendage. The mesh endothelializes over, occludes the appendage, and prevents it acting as a source of thrombus for strokes. Equivalence to warfarin has been demonstrated; however, there is a small procedural risk of stroke and tamponade.

¹ NICE 2006 guidelines for anticoagulation in AF

Table 10.2 CHADS2 scoring system to assess risk of stroke in AF^a

Condition	Score
Congestive heart failure	1
Hypertension	1
Age >75 years	1
Diabetes	1
Previous Stroke or transient ischaemic attack (TIA)	2

Patients with paroxysmal, persistent, or permanent AF with score ≥ 2 are at high risk of stroke and should receive warfarin (INR 2–3) unless there is a contraindication


^aFuster V, Ryden LE, Asinger RW, *et al* (2001). ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation. *Circulation* **104**: 2118–50.

Ventricular tachycardia

This section deals with diagnosis and pharmacological management. Mechanisms and ablation are discussed in detail in Chapter 11. The most important distinction is the presence of structural heart disease. Impaired LV function is the strongest predictor of a poor prognosis.

Normal heart VT (benign VT)

Right ventricular outflow tract (RVOT) tachycardia

This is due to automatic firing cells in the RVOT, giving a characteristic ECG pattern of LBBB with a strongly inferior axis (see Fig. 10.11). Paroxysms of palpitation are related to exercise. The tachycardia is adenosine sensitive. Symptoms are usually well controlled by verapamil or β -blocker, but RFA is a successful curative option. Care must be taken to exclude arrhythmogenic right ventricular cardiomyopathy (ARVC) as the diagnosis, particularly if the ECG or ECHO is not typical (see  p. 524). LVOT tachycardia (RBBB + inferior axis) is also recognized.

Fascicular tachycardia

Its mechanism is uncertain; however, activation emerges from the left posterior fascicle. ECG typically shows RBBB with superior axis (see Fig. 10.12). It is sensitive to IV verapamil (which normally slows then terminates it) but not adenosine. Symptoms are well controlled with oral verapamil but RFA offers a cure.

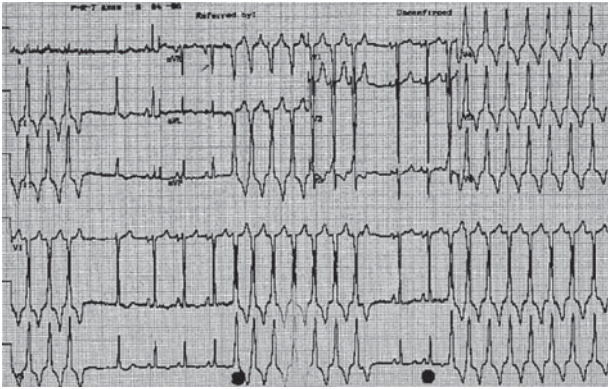


Fig. 10.11 Intermittent RVOT tachycardia and sinus rhythm. During the tachycardia beats, notice the LBBB appearance and the positivity in leads II, III and aVF, indicating an inferior axis.

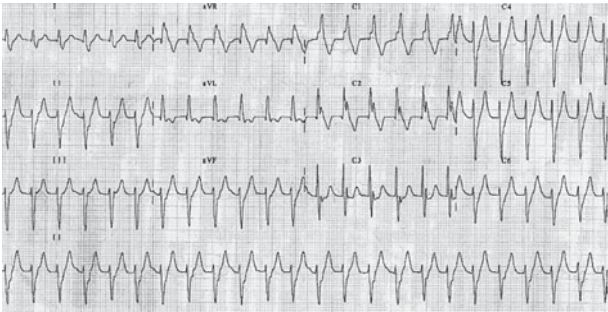


Fig. 10.12 12-lead ECG of fascicular tachycardia suggested by broad-complex tachycardia with RBBB appearance and superior axis.

VT with impaired LV function

Symptoms

Palpitations, chest pain, presyncope, syncope, dyspnoea, pulmonary oedema, and sudden death can all occur. How well patients tolerate the arrhythmia depends on their LV function and the tachycardia rate.

Aetiology

Any cause of impaired LV function can cause VT. Common causes are coronary artery disease, dilated cardiomyopathy, and HOCM. They are due to re-entry around areas of scarred or diseased myocardium. VT may rapidly deteriorate to VF and these patients die suddenly.

General management It is essential to treat the underlying heart failure and cause (angiotensin-converting enzyme inhibitors (ACE-Is, β -blockers, diuretics, nitrates, statins). This reduces not only symptoms, but also the incidence of arrhythmia.

Long-term antiarrhythmic treatment β -Blockers reduce arrhythmia and sudden cardiac death (SCD), but the impact of other drugs is minimal and often harmful. Flecainide, propafenone, and sotalol all *increase* mortality and should be avoided, except in patients with implantable cardiac defibrillators (ICDs) under supervision of an electrophysiologist. Amiodarone and mexiletine have a neutral impact on prognosis but may reduce the number of VT episodes in very symptomatic patients. RFA is only possible when VT is slow and haemodynamically well tolerated, therefore limiting its use.

Preventing SCD

ICDs have dramatically improved survival for these patients.

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Palpitations: general approach

These are a patient's awareness of their own heart beat, whether normal, too fast, too slow, or irregular.

Causes (see Table 10.3)

Palpitations is generally a benign condition, with most people presenting to a cardiologist having ectopic beats only or no underlying arrhythmia at all. Palpitations caused by ventricular arrhythmia or bradycardia are unusual but require urgent investigation and treatment. Palpitations are commonly found in patients with anxiety or depression.

Table 10.3 Causes of palpitations

Arrhythmia	Sensing own heart rhythm	Not related to heart
<ul style="list-style-type: none"> ● Atrial or ventricular ectopic beats ● AF paroxysmal or persistent ● Other supraventricular tachycardia (SVT) ● VT ● Bradycardia; AV or sinus node disease 	<ul style="list-style-type: none"> ● Normal ● Hyperdynamic circulation <ul style="list-style-type: none"> • pregnancy • hyperthyroidism • anaemia • fever ● Physiological tachycardia <ul style="list-style-type: none"> • exercise • anxiety • caffeine 	<ul style="list-style-type: none"> ● Depression ● Anxiety

Evaluation

- Elicit a careful description of the symptoms and ask the patient to tap out the rhythm on a desk. Missed beats, sudden thumps, symptoms lasting a few seconds suggest atrial or ventricular ectopics; sudden onset/offset with rapid heart beat suggest SVT; and irregularity suggests AF.
- Beware associated syncope, near syncope, or chest pain; these suggest a more sinister cause—ventricular arrhythmia or bradycardia.
- Carefully review drugs for potential causes. What is the patient's caffeine and alcohol intake?
- Look for evidence of structural heart disease (previous MI, murmur, signs of heart failure, abnormal ECG); these make ventricular arrhythmia more likely.
- Is the patient thyrotoxic?

Investigations

● 12-lead ECG	Look for tachycardia/bradycardia (see previously). Evidence of previous MI
● Blood tests	FBC (anaemia?), biochemistry, thyroid function Ca ²⁺ , Mg ²⁺ (especially if on diuretics) Biochemical markers of cardiac injury
● ECHO	Extremely helpful even if just to reassure the patient. Look for structural heart disease—old MI, dilated cardiomyopathy, hypertrophic cardiomyopathy (HCM), etc. If normal, then the prognosis is very good regardless, of arrhythmia
● Ambulatory (Holter) monitoring	Continuous recording of patient's cardiac rhythm for 24 hours, 48 hours, or 7 days. Correlate the symptom diary with rhythm. Ensure that an appropriate length of recording is used e.g. a 24-hour monitor is pointless if symptoms occur once a month!
● Event (loop) recorder	Cardiac monitor that continually records heart rhythm on a loop of 5–10 minutes but stores in memory only when activated by the patient during symptoms or if a preset heart rate is detected (e.g. >160 bpm or <40 bpm). Can be carried or worn for 2–4 weeks
● Implantable loop recorder (Reveal™)	If there are palpitations associated with syncope
● Exercise test	If palpitations are precipitated by exertion or associated with chest pain
● Electrophysiology study	When a definitive diagnosis cannot be made by other means but tachyarrhythmia is strongly suspected

Management

If an arrhythmia is identified, treat as described previously. In most people, either no abnormality or ectopic beats only will be discovered, and reassurance can be given.

Syncope: general approach

Syncope is a transient loss of consciousness (blackout) due to a disorder of the circulation. It is a medical emergency as it may be the first manifestation of an undiagnosed life-threatening condition. Causes are listed in Table 10.4 and they should be distinguished from the much rarer neurological causes of transient loss of consciousness, e.g. epilepsy.

Evaluation

A systematic process is needed to establish a cause, future risk, and the appropriate management. In 10–15%, a cause will not be found. Patients should not be discharged until a diagnosis has been established (Fig. 10.13).

- A clear history is essential, including a reliable witness account if available. Was there truly loss of consciousness? An 'aura', tongue biting, tonic–clonic episodes, incontinence (faecal more specific than urinary), paralysis, or a prolonged period of disorientation afterwards, all suggest epilepsy. An absent or minimal prodrome, preceding palpitations or chest pain, and dramatic collapse suggest arrhythmia. A clear precipitating event, e.g. pain or emotion, the description of 'clouding in' and realization of 'going to faint' suggest reflex syncope. Are symptoms postural? Carefully review medications for BP-lowering and QT-prolonging drugs.
- Examination may reveal important cardiac lesions. Check L + S BP.

Investigations

- | | |
|----------------------------------|---|
| • 12-lead ECG | Presence of arrhythmia or heart block may reveal the diagnosis. Long QT, WPW, Brugada (after flecainide infusion) are all rare causes but may be apparent. Q waves, absent R wave, T-wave abnormalities, BBB, left ventricular hypertrophy (LVH) all suggest underlying structural heart disease. Exercise ECG is indicated for exercise-related symptoms or where ischaemia is suspected |
| • ECHO | Identifying structural heart disease is the key to management of unexplained syncope. Poor LV function strongly predicts malignant arrhythmias and risk of SCD. Further investigations such as ischaemia stress testing, TOE, MR, coronary angiography, may be indicated to elucidate the diagnosis |
| • Carotid sinus massage | Simple to perform and may be diagnostic in elderly patients. A profound bradycardia and asystole may be induced. Avoid in known or suspected carotid vascular disease |
| • Ambulatory (Holter) monitoring | 24-hour ECG recording has a very low yield for identifying arrhythmia. A negative tape has no value. For patients with poor LV function, VT cannot be excluded in this way. Modern digital recorders can store 2 weeks continuously, increasing the yield |

● Implantable loop recorder (Reveal™)	For infrequent episodes (less than once a month). It is implanted under the left clavicle under local anaesthetic and continually records heart rhythm on a loop of 5–10 minutes but stores in memory only when activated by the patient, e.g. after a syncopal episode
● Head-up tilt testing	When reflex syncope is suspected, this is performed. Patients are strapped to the table and tilted at 60–80 degrees for 45 min, then if there are no symptoms, provocation can be given with glyceryl trinitrate (GTN) or isoprenaline. This will precipitate syncope in 95% of sensitive patients. Continuous beat-to-beat cardiac and BP monitoring allows precise identification of whether a heart-rate rise or fall precedes the BP drop
● Electrophysiological study	Useful for the undiagnosed but strongly suspected arrhythmia. Failure to induce VT does indicate a lower but not absent risk of future events, and therefore is of little value in determining the risk of sudden death and who should have an ICD

Table 10.4 Principle causes of transient loss of consciousness

Cardiovascular (=syncope)	<i>Reflex syncope</i> (due to neurally mediated reflexes) has various names: vasovagal ('simple faint'), neurocardiogenic syncope, carotid sinus syncope, situation-related (micturition, cough, swallow), etc.
	<i>Arrhythmia</i> : bradycardia (AV or SA nodal disease), VT, VF, torsades de pointes (long QT syndrome), WPW, SVT (rare)
	<i>Postural hypotension</i> : elderly, antihypertensive or heart-failure drugs
	<i>Mechanical problems</i> : severe valvular stenosis, HOCM, PE, pulmonary hypertension, aortic dissection
Neurological	Epilepsy, vertebrobasilar ischaemia, migraine
Psychogenic	Fictitious, hysteria, panic disorders
Other	Hypoglycaemia, hyperventilation, hypoxia

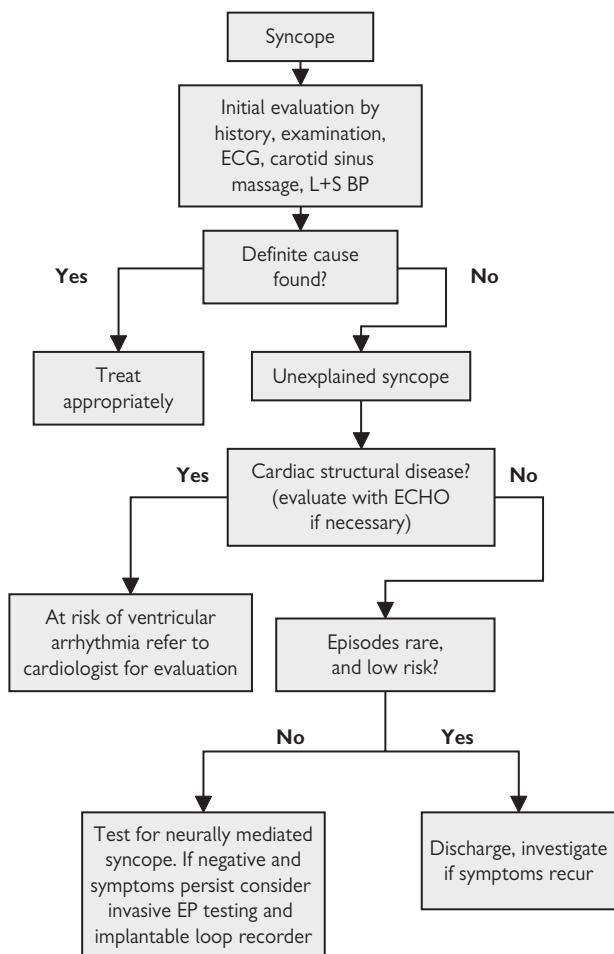


Fig. 10.13 Guidelines for evaluation of the syncopal patient. Adapted from: Guidelines on management (diagnosis and treatment) of syncope. *European Heart Journal* 2001; **22**, 1256–1306.

Syncope: management

Where a specific cause or precipitation is identified, this should be treated or avoided (e.g. pacing for heart block), See specific chapters. Other points to note follow.

Structural heart disease


Patients with syncope and poor LV function need referral to a cardiologist for consideration of ICD prescription, as there is a risk of sudden death

Neurally mediated 'reflex' syncope

Treating reflex syncope is a challenge. Lifestyle advice on avoiding precipitating events (such as prolonged standing) and good hydration may be sufficient. The use of pacemakers (dual chamber with specific rate-drop-detection algorithms) remains controversial. Asystole or severe bradycardia detected spontaneously by an implantable loop recorder is a more appropriate indication than when induced by tilt testing. Drugs tried include fludrocortisone (to expand intravascular volume), paroxetine (may interfere with the autonomic reflex arc centrally), β -blockers (to block LV stretch receptors), and midodrine (α -adrenoreceptor agonist); however, a significant evidence base is lacking.

Driving¹

The Driver and Vehicle Licensing Agency (DVLA) has set five diagnostic categories of syncope to evaluate fitness to drive, ranging from no restrictions following a vasovagal episode, 6-month licence revoke for high risk or unknown cardiovascular cases, and 12 months following a seizure event.

¹ DVLA current medical standards of fitness to drive  www.dvla.gov.uk

Inherited arrhythmia syndromes

This group of uncommon diseases attracts a great deal of public interest because of sudden deaths that occur in otherwise healthy and unsuspecting young people. The care of patients and affected families has developed into a multidisciplinary subspecialty, involving cardiologists, geneticists, and pathologists. There is an overlap with inherited disorders of heart muscle, e.g. HCM. This section focuses on those conditions with a primary electrical problem, predominantly genetic disorders of the ion channel.

Long QT syndrome

Long QT syndrome (LQTS) is an autosomal dominant condition characterized by a prolonged QT interval on the surface ECG that predisposes to ventricular arrhythmias, syncope, and SCD. The disease may present in fetal life, although genetically affected individuals may remain asymptomatic lifelong. It is estimated that LQTS affects ~1:2500 of the population. At a molecular level, genetically encoded mutations in either sodium or potassium ion channels lead to a prolongation of ventricular repolarization and hence QT prolongation. Over the last 15 years, the genes encoding both potassium and sodium channels have been identified, enabling a better understanding of the transition from genetic and molecular anomalies to cardiac phenotype

Cellular pathology

The initial phase (phase 0) of the cardiac action potential (AP) is determined by cellular depolarization via rapid sodium influx (I_{Na}), whereas potassium efflux governs repolarization, further divided into the slow (I_{ks}) and rapid (I_{kr}) components of the delayed rectifier current, which determine phase 2 and 3 of cardiomyocyte repolarization respectively. Potassium channel mutations lead to a loss of channel function and hence directly delay repolarization and restoration of the resting myocyte voltage through a slowed K^+ efflux. Mutations in either the slow or rapid component of the delayed rectifier current lead to LQTS. Conversely, gain-of-function mutations within the sodium channel facilitate a persistent late, slow I_{Na} and thereby prolongation of depolarization and delayed repolarization. The net effect of either excessive I_{Na} or reduced I_k is to prolong the positive charge within the cell and cellular repolarization, which manifests on the surface ECG as prolongation of the QT interval. QT prolongation and the associated after-depolarizations during critical periods in ventricular repolarization create a short-long-short appearance on the ECG ultimately, and may precipitate torsades de pointes (Fig. 10.15), a polymorphic VT that is the hallmark arrhythmia of QT prolongation.

Congenital LQTS: clinical features

Congenital LQTS was initially subdivided into two eponymous syndromes; autosomal dominant Romano–Ward syndrome, and the much rarer autosomal recessive Jervell–Lange–Nielsen syndrome, which is associated with sensorineural deafness and a severe cardiac phenotype. This classification has now been superseded by different LQTS subtypes based on

the associated genetic and channel mutation (see Table 10.5). Long QT1 is classically associated with syncope or cardiac arrest (due to ventricular arrhythmias) during exercise, particularly swimming, whereas in long QT2, symptoms relate to sudden emotional or auditory stimuli, especially if suddenly waking from sleep. Women with long QT2 experience an increased frequency of symptoms in the first 9 months post-partum. Conversely, symptoms in long QT3 are typical at lower heart rates during sleep and rest, and although the frequency of symptoms is lower, the rate of sudden death is much higher. Symptoms of LQTS are misdiagnosed as epilepsy, vasovagal syncope, or breath-holding attacks, with potentially fatal consequences.

Acquired LQTS (see Table 10.5)

QT prolongation may result from cranial trauma, severe hypothermia, electrolyte disturbance, bradycardia, and numerous pharmacological agents. These features may precipitate ECG changes and symptoms in patients with latent congenital LQTS. All patients with the congenital form of the disease should be given a list of drugs that must be actively avoided (www.azcert.org).

Investigation and risk stratification

The diagnosis of LQTS is based on the clinical history and ECG. The QT interval should be measured in lead II or V₅ and should be corrected for heart rate according to Bazett's formula; $QT_c = QT / \sqrt{RR}$ (see Fig. 10.14). Risk stratification is based on age, sex, QT interval, recent symptoms, and genetic diagnosis.

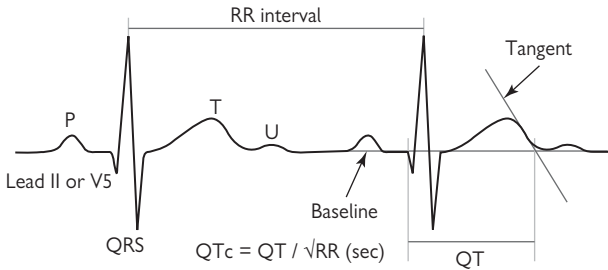


Fig. 10.14 QT interval is measured in lead II or V₅ from the point of the first sharp deflection away from the baseline of the QRS interval to the end of the T wave, defined as the intersection of the baseline and a tangent drawn to the steepest slope of the last limb of the T wave. Reproduced with permission from Postema et al. (2008). *Heart Rhythm* 5: 1015–18.

Long QT syndrome, continued

Table 10.5 Characteristics of currently identified congenital LQTS

LQTS	Mutation	Ion current ^a	Effect of mutation	Clinical features
I	<i>KVLQT1</i> (CW11)	I_{ks}	Loss of function	Exercise-related syncope
II	<i>HERG</i> (CW7)	I_{kr}	Loss of function	Syncope related to sudden emotional or auditory stress
III	<i>SCN5A</i> (CW3)	I_{Na}	Gain of function	Symptoms at rest rather than when excited. Young age and usually presents as sudden death
IV	<i>Ankyrin-B</i> (CW4)	See below	Loss of function	—
V	<i>KCNE1</i> (CW21)	I_{ks}	Loss of function	—
VI	<i>KCNE2</i> (CW21)	I_{kr}	Loss of function	—

^aPotassium currents (I_k) are repolarizing and the sodium currents (I_{Na}) depolarizing. The ankyrin-B gene codes not for an ion channel but for a cellular structural protein that binds sodium ion channels (Splawski I, Shen J, Timothy KW, et al. (2000). Spectrum of mutations in Long-QT syndrome genes. *Circulation* 102: 1178–85.)

Common causes of acquired LQTS

Drugs*

- **Antiarrhythmics:** quinidine, procainamide, disopyramide, flecainide, propafenone, sotalol, ibutilide, dofetilide, amiodarone (rare)
- **Antimicrobials:** erythromycin, clarithromycin, trimethoprim, ketoconazole, itraconazole, chloroquine
- **Antihistamines:** terfenadine
- **Other drugs:** amitriptyline, fluvoxamine, chlorpromazine, domperidone, cisapride, glibenclamide.

Electrolyte imbalance

- Hypokalaemia, hypomagnesaemia, hypocalcaemia.

Severe bradycardia

- Complete heart block, sino atrial node disease, hypothyroidism, hypothermia.

* Note this is not a comprehensive list and LQTS is the commonest single reason for new drugs being withdrawn. When a patient is known to be at risk from LQTS or there is concern that interaction may occur with other QT-prolonging drugs, all drugs and potential interactions.



Fig. 10.15 Torsades de pointes. A continuous tracing from three leads of a patient monitored on CCU. The first complex is a sinus beat followed by two ectopics. There is then a long pause (2 s) followed by another sinus beat.

Long QT syndrome: management

Torsades de pointes (TDP) usually terminates spontaneously, although it may degenerate to VF. A prolonged episode causing cardiovascular compromise needs immediate DC cardioversion. For recurrent bursts or following a cardiac arrest, use IV magnesium bolus and infusion, followed by urgent temporary pacing (at rate 90–110/min) if necessary.

Acquired LQTS

The underlying cause should be identified and reversed. Stop offending drugs. Give Mg^{2+} before getting blood results. K^+ can be checked rapidly with a blood gas analyser, replace if less than 4 mmol/L, and aim to achieve high normal levels. An isoprenaline infusion can be commenced while waiting to pace. Long-term treatment is not usually necessary; however, a permanent pacemaker is required if non-reversible heart block was the cause.

Congenital

As most events are triggered by sudden increases of sympathetic activity, treatment is aimed at preventing this. Beta-blockade is the mainstay and is especially effective in LQT1, although less so in LQT3. Patients should avoid precipitating symptoms. Cardiac pacing is useful to alleviate the β -blocker-induced bradycardia, and, where pauses have been identified, to precipitate symptoms (LQT3). ICDs should only be used with careful consideration, i.e. for patients at high risk of SCD or where a resuscitated cardiac arrest was the first event. ICDs prevent SCD but not TDP, and recurrent distressing shocks for non-sustained episodes can ruin a patient's life. Careful patient selection, concomitant use of β -blockers, and shrewd device programming minimizes inappropriate therapies. In resistant cases, or where ICD is contraindicated, left cardiac sympathectomy may be highly effective.

Asymptomatic patients

Once a diagnosis of LQTS has been made, screening should be offered to all family members. Screening (clinical and/or genetic) of affected families reveals patients with LQTS who have never had symptoms and may have normal QT intervals. All patients must be carefully evaluated and the risk determined on an individualized basis. Most patients do not die from LQTS but all are at risk (13% incidence of fatal events over a lifetime if untreated). A balance must be struck between lifelong treatment with side-effects and the spectre of sudden death.

Further reading

Priori SG, Schwartz PJ, Napolitano C, et al (2003). Risk stratification in the long-QT syndrome. *N Engl J Med* **348**: 1866–74.

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Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is an autosomal dominant disorder characterized by fibrofatty infiltration of ventricular myocardium, which classically affects the right ventricle but may also show biventricular involvement. ARVC predominantly relates to genetically encoded abnormalities in the desmosome, a transmembrane assembly of proteins involved in intercellular adhesion and communication. The disease is progressive and may be notoriously difficult to diagnose in its early phases. Diagnosis is made according to international criteria based on electrocardiography, echocardiography, cardiac MR, and histology (see Table 10.6).

Ventricular arrhythmia typically show a left bundle morphology that is indicative of a right ventricular origin, often relating to areas of scar within ventricular myocardium. In sinus rhythm, the ECG may show a broadened QRS and T-wave inversion in leads V_1 – V_3 , and epsilon waves indicating late ventricular activation. The predominant risk is arrhythmia, although a small proportion of patients progress to heart failure requiring transplantation.

Drug management includes β -blockers, sotalol, amiodarone, and class 1 agents in those with preserved LV function, although as they have limited potential in preventing SCD, an ICD is warranted in high-risk cases. VT ablation may be acutely successful, but due to continual disease progression, the rate of recurrence is high. Genetic analysis for mutations in the five major desmosomal proteins should be performed in those with clinical or familial evidence of the disease.

Table 10.6 Diagnostic criteria for arrhythmogenic right ventricular tachycardia

	International Task Force Criteria 1994 ^a		Modified Task Force Criteria 2002 ^b
	Major	Minor	Confirmed case of familial ARVC in first-degree relative, plus one of:
Structural abnormalities	Severe RV dilatation and reduction of ejection fraction (EF)	Mild RV dilatation and reduction of EF	Mild RV dilatation and reduction of EF
	Localized RV aneurysms	Regional RV hypokinesia	Regional RV hypokinesia
	Severe RV segmental dilatation	Mild RV segmental dilatation	Mild RV segmental dilatation
Tissue characterization	Fibrofatty replacement of myocardium on biopsy		
Repolarization abnormalities	T-wave inversion in V ₂ and V ₃ (>12 years of age and without bundle branch block)		T-wave inversion in V ₂ and V ₃ (>12 years of age and without bundle branch block)
Depolarization abnormalities	Epsilon waves	Late potentials on signal-averaged ECG	Late potentials on signal-averaged ECG
	Localized QRS prolongation in V ₁ -V ₃		
Arrhythmia		>1000 ventricular ectopics/24 hours on Holter monitor	LBBB VT
		LBBB VT	>200 ventricular ectopics/24 hours on Holter monitor
Family history	Familial disease confirmed on post-mortem or at surgery	Family history of sudden cardiac death due to suspected ARVC	
		Family history of confirmed ARVC	

^aAdapted from McKenna WJ et al (1994). Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Br Heart J* 71: 215-18.

^bAdapted from Hamid MS et al (2002). Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. *J Am Coll Cardiol* 40: 1445-50.

Brugada syndrome

Brugada syndrome is an increasingly recognized cause of SCD, characterized by a pattern of J-point elevation >2 mm in leads V_1 – V_3 . The heart is structurally and functionally normal. Approximately 30% of patients will have identifiable mutations in the sodium channel gene (*SCN5A*). The disease is especially prevalent in South-East Asian individuals, and shows both age- and sex-related penetrance, classically presenting in males (M:F 8:1) in their 30s and 40s. Symptoms include syncope and VF leading to cardiac arrest, although the ECG findings may be incidental.

A type 1 pattern (coved ST elevation >2 mm and inverted T wave) in ≥ 1 anterior precordial leads (V_1 – V_3) is diagnostic, although these changes are dynamic. Conditions that should be actively excluded are atypical RBBB, acute MI, pericarditis, ARVC, and autonomic and electrolyte disturbances. Type 2 (saddle-back ST segment elevation ≥ 1 mm) and type 3 ECG (saddleback/coved ST segment <1 mm) are non-diagnostic but suggestive of Brugada syndrome, and may be converted to a diagnostic type 1 pattern using a class 1 antiarrhythmic agent challenge: ajmaline 1 mg/kg IV to max 50 mg; flecainide 2 mg/kg IV, or procainamide 10 mg/kg IV (see Fig. 10.16). Similarly, a diagnostic ECG may be precipitated by fever and different medications including class 1 antiarrhythmics, anti-depressant, antipsychotics, and cocaine.

Patients with symptomatic Brugada syndrome (syncope, VT, VF) should undergo ICD implantation. No medical therapy is effective, although quinidine is under investigation. The role of programmed ventricular stimulation to identify high-risk, asymptomatic patients who should undergo primary prevention ICD implantation remains controversial.

Catecholaminergic polymorphic VT

Catecholaminergic polymorphic VT (CPVT) is an aggressive condition characterized by adrenergically stimulated polymorphic VT. Genetically encoded mutations in the cardiac ryanodine receptor (autosomal dominant) or calsequestrin (autosomal recessive) lead to abnormalities in myocardial calcium flux, which, in the presence of catecholamines, trigger delayed afterdepolarizations and VT. Patients present with palpitations, syncope, or cardiac arrest during exercise or emotional stimulation, often in the first two decades of life. Baseline ECG and echocardiogram are normal. Investigations include exercise testing, Holter monitoring, and adrenaline provocation that reveal the classical bidirectional or polymorphic VT, usually once the heart rate reaches 110–120 bpm. β -blockers are the mainstay of therapy, although verapamil and flecainide have also been used. Given the highly aggressive nature of the disease, ICD implantation should be considered in patients with symptoms or persistent VT despite appropriate drug therapy.

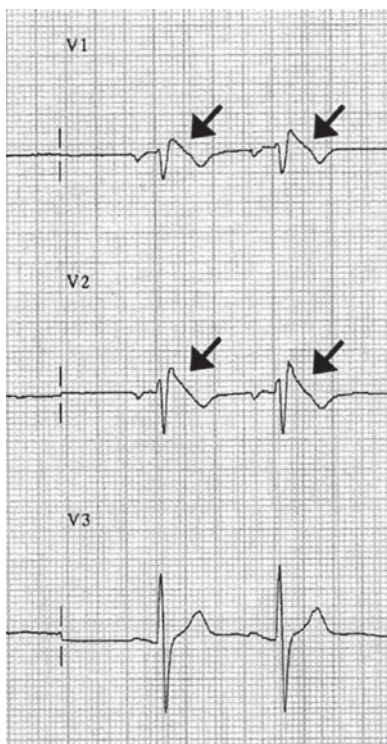


Fig. 10.16 Brugada ECG with flecainide challenge. A typical Brugada ECG with arrows marking the characteristic prominent coved ST-segment elevation in the right precordial leads, ≥ 2 mm at its peak followed by a negative T wave with little or no isoelectric separation. Intravenous administration of either ajmaline (1 mg/min) or flecainide (2 mg/kg, max 150 mg; in 10 minutes) exaggerate the ST changes or reveals them if initially absent.¹

¹ Wilde AA, Antzelevitch C, Borggrefe M, et al. (2002). Proposed diagnostic criteria for the Brugada syndrome. Consensus report. *Circulation* **106**: 2514–19.

Arrhythmia in special situations

Paediatrics

Arrhythmia may occur at any stage in the paediatric population, from fetal life to adolescence.

Fetus and neonate

AVRT and atrial flutter are the usual cause of tachycardia. If persistent, *hydrops fetalis* may result. The majority of AVRT resolves spontaneously *in utero* or by one year of age, although recurrences later in life may occur. Ablation is rarely necessary. Congenital heart block occurs mediated by maternal anti-Ro/SSA antibodies, and, if severe, may also cause *hydrops fetalis*. This always persists after birth and usually requires permanent pacing, although timing depends on the stability of the subsidiary pacemaker.

Infancy and childhood

AVRT is the usual (80%) cause of tachycardia. AVNRT is rare in infancy, but becomes increasingly common in teenage years. Focal atrial tachycardias and a specific form of AVRT mediated by a slow atrial septal accessory pathway (persistent junctional reciprocating tachycardia) both lead to incessant tachycardia and profound ventricular dysfunction (tachycardia cardiomyopathy). This completely resolves with successful therapy. Radiofrequency ablation is now commonly performed in older children, and may also be used in refractory arrhythmias in neonates and young infants when necessary.

Congenital heart disease

Arrhythmias in association with congenital cardiac lesions are poorly tolerated, and, if uncontrolled, may lead to a rapid decline in ventricular function and cardiac output.

Supraventricular tachycardia

This is a major cause of both morbidity and mortality in congenital heart disease. Accessory pathways are associated with Ebstein's anomaly and congenitally corrected transposition of the great arteries, and this results in AVRT. Macro-re-entrant atrial tachycardia is common, late, following the Mustard or Fontan procedure. This is notoriously difficult to control with medication, and although ablation (either percutaneous or surgical) is commonly successful acutely, arrhythmia recurrence is a problem.

Ventricular tachycardia

VT is seen in Ebstein's anomaly and following repair of tetralogy of Fallot. Treatment may involve either RFA or an ICD.

Pregnancy

The haemodynamic and hormonal changes associated with pregnancy may unmask arrhythmic substrates for the first time, or exacerbate pre-existing arrhythmic conditions. Gestational palpitations are common, and, most frequently, an increased awareness of physiological tachycardia. If new ventricular arrhythmias occur, peripartum cardiomyopathy should be actively excluded.

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Permanent pacemakers

Introduction

Permanent pacemakers play a central role in the management of bradycardia. In addition, they can be used to treat atrial and ventricular tachyarrhythmias (with ICDs), as well as to improve ventricular function and symptoms in heart failure (cardiac resynchronization therapy). Basic pacemaker function involves sensing and pacing either the atria or ventricles or both.

International code

This is a three-letter identification code describing the basic function of the pacing system. The first letter is the chamber(s) paced and the second letter is the chamber(s) sensed. V = ventricle, A = atrium, D = dual (i.e. A+V). The third letter is how the device responds to a sensed event. I = inhibits, T = triggers, D = dual (i.e. I+T), and O = nothing. Often a fourth letter is used to describe added features of the device e.g. R = rate response.

Implantation

- *Antibiotic prophylaxis*: reduces risk of infection. Use a drug that is effective against staphylococci, e.g. flucloxacillin (clarithromycin or clindamycin if penicillin allergic)
- *Site of implant*: usually infraclavicular (right or left); rarely, abdominal, axillary, or submammary
- *Pocket*: subcutaneous or submuscular (beneath pectoralis major)
- *Venous access*: direct cutdown to the cephalic vein in the deltopectoral groove or Seldinger approach to the subclavian vein. A venogram (from the ipsilateral brachial vein) is useful if access is difficult. Rarely, internal jugular or femoral veins are used
- *Leads*: active (screw-in) or passively fixed. Use an active fixation lead in the atrium post cardiac surgery
- *Lead placement*: RV apex/septum for the ventricular lead. RA appendage for atrium. See Fig. 10.17 for lead placement, and Table 10.7 for acceptable parameters
- *Suturing*: lead sleeves should be firmly stitched to muscle with a non-resorbable suture (silk, surgilon). The pocket is closed in layers with vicryl. Skin closure is with prolene or Dermabond glue
- *Follow-up*: ensure stitches are removed and the wound is healed. Pacing check within 1 month (see later).

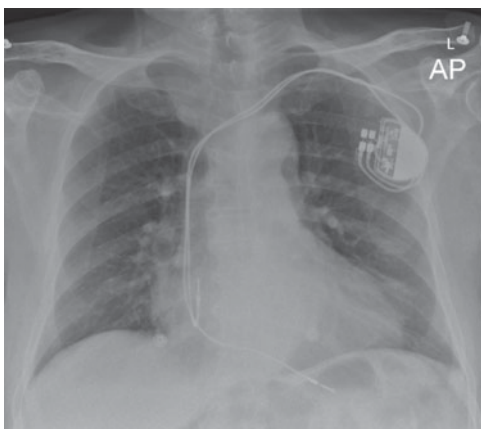


Fig. 10.17 AP chest X-ray post permanent pacemaker implantation showing satisfactory placement of actively fixed leads into the right atrial appendage and right ventricular apex. The generator has been placed subcutaneously in the standard left infraclavicular position.

Indications for permanent pacing

Class I

- Sinus node disease with symptoms due to bradycardia, pauses, or chronotropic incompetence
- Third-degree or second-degree (Mobitz type 2) AV nodal heart block
- Persistent AF and asymptomatic pauses ≥ 5 s
- Pause-dependent VT (e.g. LQTS)
- Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and when carotid sinus pressure induces ventricular asystole >3 s

Class IIa

- Symptomatic sinus node disease with heart rate <40 bpm or unexplained syncope
- First- or second-degree heart block causing pacemaker syndrome
- Chronic bifascicular block and unexplained syncope when other causes including VT have been excluded
- High-risk patients with LQTS
- Hypertrophic cardiomyopathy with symptoms due to outflow tract obstruction refractory to medical therapy

Adapted from ACC/AHA/HRS 2008 guidelines. *J Am Coll Cardiol* 51:2085–105.

Table 10.7 Acceptable pacing parameters for new leads

	Atrium	Ventricle
Threshold ^a	<1.5 V	<1.0 V
Sensitivity	>1.5 mV	>4.0 mV
Slew rate	>0.2 V/s	>0.5 V/s
Impedance	400–1000 ohms	400–1000 ohms

^aUsing a pulse width of 0.5 ms.

Which pacing modality?

The vast majority of patients should have an atrial-based pacing (i.e. either AAI or DDD). Ventricular-only pacing leads to a greater incidence of AF and potential pacemaker syndrome (see Fig. 10.18).

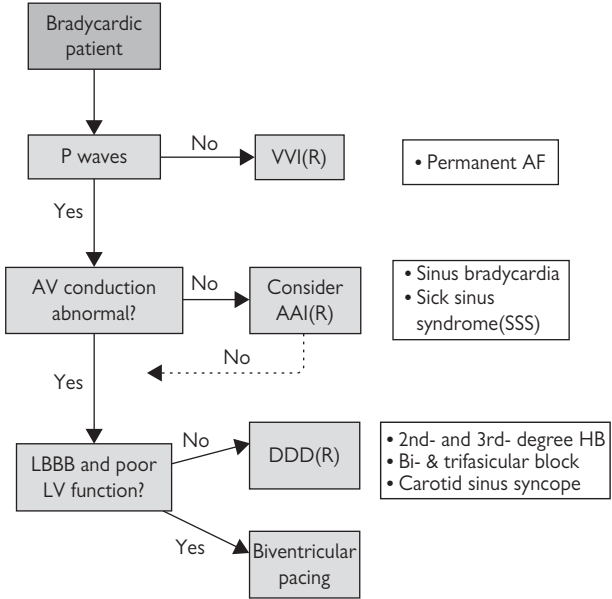


Fig. 10.18 Which pacing modality?

Complications of pacing

At the time of implantation

The procedural complication rate is 5%. Important complications are:

- *haematoma*: most can be managed conservatively, but evacuation is required if very large or threatening the skin (usually due to an arterial bleed). Meticulous haemostasis should be secured during the implant, and diathermy used if necessary. Bruising over the site is common, and resolves spontaneously
- *pneumothorax*: a small apical pneumothorax can be observed with serial X-rays. A chest drain is required for anything larger. A haemothorax may co-exist
- *pericardial effusion*: more common with actively fixed leads, which can perforate through the thin-walled RA or RV (right ventricle). Pericardial tamponade can occur, requiring urgent pericardiocentesis
- *infection*: occurs at the time of implant but usually presents late. Minimized by aseptic technique and antibiotic prophylaxis
- *air pulmonary embolism*: care must be taken when using sheaths, as a significant volume of air can be drawn into the vein
- *axillary vein thrombosis*: rare, can present with a swollen arm and is treated with systemic anticoagulation.

Late complications

- *Lead displacement*: this is common and requires lead repositioning.
- *Infection*: risk factors are fever within 24 h of implant, use of a temporary wire, prolonged procedure, any revision procedure shortly after the first implant. Infection can manifest as localized pocket abscess/cellulitis, septicaemia, or endocarditis with vegetations on leads. Treatment is urgent extraction of the entire system. Prolonged intravenous antibiotic therapy may be needed. Patients who are pacing dependent will need a temporary wire. New device implantation should be performed when there are no signs of infection on the contralateral site.
- *Box or lead erosion*: at implant, care must be taken to create a large enough pocket for the device and leads without causing tension on the skin. Indolent infection can cause erosion. If the skin is threatened, box repositioning may be attempted (to a submuscular pocket), but if the skin is breached the whole system needs to be explanted.
- *Lead damage/failure*: common causes are crush between the clavicle and first rib, or in the pocket if the leads have been over-coiled tightly. Fibrosis at the lead tip results in higher pacing thresholds and poor sensing. Lead failure requires insertion of a new lead (see Fig. 10.19).
- *Device failure* is rare.
- *Venous obstruction*: this is usually asymptomatic (due to collateral formation) but may present a problem at system revision.

Other problems

- *Pacemaker syndrome*: this occurs in patients who have sinus node function but are implanted with a VVI pacemaker. Symptoms include; presyncope, syncope, lightheadedness, fatigue, exercise intolerance, malaise, lethargy, and dyspnoea. It is due to independent atrial and ventricular contraction. The treatment is to restore AV synchrony, by either reducing the pacing rate or inserting an atrial lead.
- *Endless loop tachycardia*: this occurs in dual chamber pacing (VDD, DDD, or DDDR) and is caused by inappropriate sensing of retrograde P waves and hence triggering a ventricular response. The treatment is to increase the post-ventricular atrial refractory period (PVARP) so as not to sense the retrograde P wave.
- *Atrial tachycardias* can cause rapid ventricular pacing in dual-chamber systems by sensing the atrial rate. To overcome this, the pacemaker can either mode-switch to VVI or be reprogrammed to DDI mode.

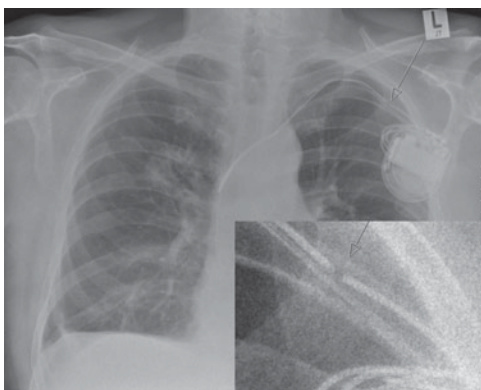


Fig. 10.19 Atrial lead fracture. A dual-chamber ICD was implanted 3 years prior to this PA CXR. At routine follow-up, the pacing impedance was very high and there was no atrial sensing or capture. The atrial lead has fractured (arrow). The inset shows a magnified view of the fracture (arrow).

Pacemaker follow-up

Magnet response

When the pacemaker is within a sufficiently strong magnetic field, it reverts to its magnet mode. This is non-sensing fixed pacing at the device's 'magnet rate' usually 70–80/min, i.e. DOO (dual chamber) or VOO/AOO (single chamber). Application of a magnet over the pacemaker can be used during surgery to prevent device inhibition (and hence asystole) when diathermy is being used.

Pacemaker clinic

The device is interrogated every 6–12 months. At these visits, the function of the lead(s) is assessed by checking the pacing threshold, sensitivity (the size of sensed electrogram detected), and pacing impedance. Any change in these parameters could indicate a problem, e.g. a low impedance suggests an internal insulation break, while a high impedance might suggest a lead fracture. The battery voltage is measured, and below a critical level the elective replacement indicator (ERI) activates. There is approximately 6 months between ERI and the dangerous EOL (end of life). A box change is usually arranged at the ERI time.

Interference

- *Magnetic resonance imaging (MRI)*: absolutely contraindicated in a patient with a pacemaker or ICD, as it can cause device malfunction and harm the patient. MRI-'safe' pacemaker systems are available.
- *Radiotherapy*: can damage pacemaker electronics or result in erosion of the generator. The damage is cumulative and the device should be shielded. Occasionally, the generator may need to be repositioned if it overlies a tumour (e.g. lung cancer).
- *Diathermy*: may inhibit pacing. The device should be reprogrammed to a non-sensing mode (VOO) prior to surgery or have a magnet applied during surgery. The pacemaker needs to be checked after surgery to ensure normal function.
- *Security gates*: these will be activated by pacemakers. Patients are advised to carry their identification card so that they can show staff.

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Cardiac resynchronization therapy

Patients with heart failure and broad LBBB on their ECG will have uncoordinated contraction and relaxation of the ventricles because of the delayed and heterogenous depolarization of the LV. This is termed dys-synchrony. By pacing the RV and LV simultaneously, cardiac resynchronization therapy (CRT) improves co-ordinated ventricular contraction, increases cardiac output, and reduces heart failure symptoms.

Electrical or mechanical dys-synchrony?

Accurate assessment of mechanical dys-synchrony by detailed echocardiography, including tissue Doppler, does not predict reliably who will respond to CRT, and therefore electrical dys-synchrony, i.e. LBBB on ECG, remains the standard measurement. CRT in patients with narrow QRS complexes even with evidence of mechanical dys-synchrony is controversial.

Implantation

The RA and RV leads (often an ICD lead) are inserted conventionally. The LV is paced epicardially via the coronary sinus (CS). Using a Seldinger technique, a guide catheter is introduced into the RA via the subclavian vein. The CS is intubated and a venogram performed to identify a suitable lateral tributary. The pacing lead is then inserted either with a stylet or using the over-the-wire technique, into a stable position with acceptable pacing parameters and no diaphragmatic stimulation (see Fig. 10.20). There are a number of tools to help place the lead, e.g. subselector sheaths, and different leads, e.g. steerable or 'active' fixation. If the anatomy is unfavourable (tortuous, small veins) or there is inability to capture the LV, patients can be referred to a cardiac surgeon for thoracoscopic-guided epicardial lead placement.

Effects of CRT

Some patients respond immediately, while the majority respond over a course of weeks. Benefit can be dramatic, with a major improvement to quality of life, reduced hospitalizations, and improved prognosis. There are improvements in LVEF and a reduction in ventricular dimensions (reverse remodelling). Indeed, implantation of devices in asymptomatic patients can delay symptom onset and reduce future hospitalization episodes for heart failure.¹

Non-responders

Unfortunately, 30–40% of patients who undergo CRT implantation fail to respond. Reasons for this are: suboptimal lead position, end-stage heart failure (New York Heart Association (NYHA) IV), alternative causes of symptoms (e.g. chronic obstructive pulmonary disease (COPD)). There are a number of options for these patients:

- *ECHO-guided optimization*: cardiac output is assessed for different AV and RV–LV pacing intervals, with the optimal settings chosen

¹ Moss AJ, Hall WJ, Cannom DS, et al. (2009). Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* **361**:1329–38.

- *lead repositioning*: the LV lead can be placed at a different site, or the RV lead moved, e.g. from the apex to the septum
- *multisite pacing*: implanting an additional LV lead via another CS branch, or if this is not possible, then two RV leads can be implanted (apex and high septum).

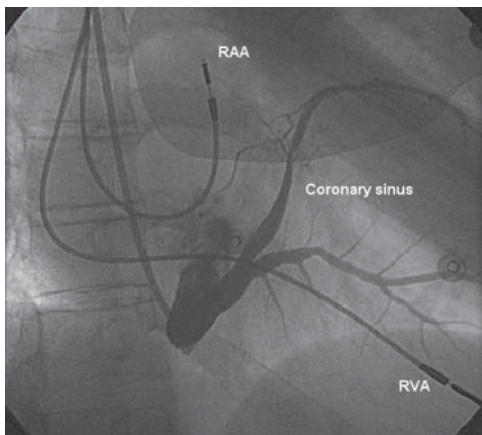


Fig. 10.20 A fluoroscopic image of the heart from the RAO projection. There is an active fixation lead in the conventional right atrial appendage (RAA) and a lead in the right ventricular apex. Dye has been injected from below retrogradely up the CS to demonstrate the lateral left ventricular branches, from where pacing stimuli can capture the ventricle.

Current indications for CRT

Class I

- NYHA class III–IV heart failure established on optimal medical therapy. Sinus rhythm with QRS duration >120 ms and left ventricular ejection fraction (LVEF) $\leq 35\%$

Class IIa

- NYHA class III–IV heart failure established on optimal medical therapy. AF with QRS duration >120 ms and LVEF $\leq 35\%$. AV nodal ablation to control the ventricular rate may be needed
- NYHA class III–IV and LVEF $\leq 35\%$ in patients who require frequent RV pacing

Class IIb

- NYHA class I–II, LVEF $\leq 35\%$ in patients who are undergoing permanent pacemaker implantation who will require frequent RV pacing

Adapted from ACC/AHA/HRS 2008 guidelines. *J Am Coll Cardiol* 51: 2085–105.

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Invasive electrophysiology

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Abbreviations

3D	three dimensional
ACT	activated clotting time
AD	afterdepolarization
AF	atrial fibrillation
AICD	automated implantable cardioverter defibrillator
AP	accessory pathway
ASD	atrial septal defect
ATP	antitachycardia pacing
AV	atrioventricular
AVN	atrioventricular node
AVNERP	atrioventricular nodal effective refractory period
AVNRT	atrioventricular node re-entrant tachycardia
AVRT	atrioventricular re-entrant tachycardia
AWCL	anterograde Wenckenbach cycle length
BBB	bundle branch block
BP	blood pressure
CFAE	complex and fractionated atrial electrogram
CS	coronary sinus
CT	computed tomography
DVT	deep vein thrombosis
ECG	electrocardiogram
EP	electrophysiology
ERP	effective refractory period
FAT	focal atrial tachycardia
FFP	fresh frozen plasma
HCM	hypertrophic cardiomyopathy
HRA	high right atrium
HSVPB	His syndrome ventricular premature beat
IAP	incremental atrial pacing
ICD	implantable cardiac defibrillator
ICegram	intracardiac electrogram
IVC	inferior vena cava
IVP	incremental ventricular pacing
LA	left atrium
LAA	left atrial appendage
LAO	left anterior oblique
LBBB	left bundle branch block
LIPV	left inferior pulmonary vein
LSPV	left superior pulmonary vein

LV	left ventricle
MI	myocardial infarction
MRI	magnetic resonance imaging
MV	mitral valve
NYHA	New York Heart Association
PE	pulmonary embolism
PV	pulmonary vein
RAO	right anterior oblique
RF	radiofrequency
RSPV	right superior pulmonary vein
RVA	right ventricular apex
RVOT	right ventricular outflow tract
RWCL	right Wenckenbach cycle length
SA	sinoatrial
SAN	sinoatrial node
SCD	sudden cardiac death
SR	sinus rhythm
SVC	superior vena cava
SVT	supraventricular tachycardia
TIA	transient ischaemic attack
TOE	transoesophageal echocardiography
TV	tricuspid valve
VERP	ventricular effective refractory period
VF	ventricular fibrillation
V/Q	ventilation–perfusion
VT	ventricular tachycardia
WCL	Wenckenbach cycle length
WPW	Wolff–Parkinson–White (syndrome)

Mechanism of tachycardias

Knowledge of how arrhythmias are initiated and perpetuated is fundamental to understanding the techniques described in this chapter.

The electrical wavefront

The excitable impulse is generated at the cell membrane by the action potential. As one cell depolarizes, it causes a reduction in negativity of the resting potential in the adjacent cell such that it this cell also reaches the threshold potential and depolarizes. The shape, orientation, and presence of gap junctions between myocardial cells allow rapid progression of this depolarization, which can be described as an electrical *wavefront*. After a cell has depolarized, it cannot depolarize again until a fixed period of recovery time has passed, the *refractory period*. Cells that are able to depolarize are *excitable* and those that cannot are *refractory*.

In sinus rhythm (SR), the source of these wavefronts is the sinoatrial node (SAN), and they may be modulated between the atrium and ventricle by the atrioventricular (AV) node. They are initiated (and therefore the heart rate is controlled) by regulation from the autonomic nervous system and circulating catecholamines. This control is lost in tachyarrhythmia, and heart rates are inappropriate.

Conduction block

A wavefront will propagate as long as there are excitable cells in its path. Anatomical barriers such as the mitral valve annulus, vena cava, aorta, etc. do not contain myocardial cells and therefore the progression of wavefronts is halted there. This is described as *fixed conduction block*, as block is always present. Dead cells are another important source of fixed conduction block e.g. the left ventricular scar of a myocardial infarction (MI).

Functional conduction block describes the situation when block is only present under certain conditions. An example is myocardial ischaemia, which may alter the electrical properties of myocytes so that they do not conduct. It is also functional block that prevents a wavefront turning back on itself, as the cells behind the leading edge are temporarily refractory and force the wavefront to continue in one direction. Other causes of functional block are: cyanosis, myocardial stretch, rate of wavefront, and direction of wavefront.

Arrhythmia mechanism

Three distinct mechanisms are described:

- enhanced automaticity
- re-entry
- triggered activity.

The first two account for nearly all clinical tachycardias, and their characteristics are compared in Table 11.1.

Table 11.1 Characteristics of automatic and re-entry tachycardias^a

	Automatic	Re-entry^a
Autonomic sensitivity? (e.g. to exercise, emotion)	Often	Unusual
Reproducible induction and termination by programmed pacing?	No	Yes
Entrainment of the tachycardia by pacing (p)?	No	Yes
Induced by atropine/isoprenaline infusion?	Yes	May augment induction by pacing ^a
Related to metabolic causes	Often	Unusual
Onset/offset	May be gradual (warm up and down)	Sudden
Specific tachycardias caused	Focal atrial tachycardia, RVOT VT	Macroreentrant atrial tachycardia, AVNRT, AVRT, VT

^aThe conduction properties of, e.g. the AV node, are influenced by autonomic tone. Spontaneous or drug-induced changes in this may then influence the development of re-entry tachycardias such as AV-nodal re-entry tachycardia (AVNRT); AF (atrial fibrillation); AVRT (atrioventricular re-entrant tachycardia); RVOT (right ventricular outflow tract); VT (ventricular tachycardia).

Mechanism of arrhythmias

Enhanced automaticity

If a nidus of myocardial cells depolarizes faster (rapid phase 4 of the action potential) than the SAN, they will act as the source of wavefronts that conduct through the heart. They may be atrial or ventricular, but if they occur in the atria they will override the SAN. As they occur from a single site they are often termed *focal*. Common sites are where myocardial cells suddenly change shape/size or those under abnormal pressures such as; the junction of veins/atrium (superior vena cava (SVC), pulmonary veins (PVs)), crista terminalis, coronary sinus (CS), AV node area, mitral/tricuspid ring, ventricular outflow tracts.

Re-entry

Re-entry accounts for >75% of clinical arrhythmias. It is caused by a perpetually propagating wavefront that it is constantly meeting excitable myocardium. For re-entry to occur, at least two distinct pathways must exist around an area of conduction block. This is best described using the example of VT due to re-entry around a LV myocardial scar (see Fig. 11.1).

1. A myocardial scar acts as an area of block, around which a normal sinus wavefront passes via normal myocardium (A) and slowly through it via diseased myocardium (B)—hence there are two distinct pathways.
2. The sinus beat is followed closely by a ventricular ectopic, which is conducted around A normally but is blocked in B, which is still refractory following the last sinus beat.
3. The distal end of B, however, is now excitable and the wavefront passes backwards up B, which has had time to fully recover by the time it reaches the proximal end. Conduction is sufficiently slow up B that now A is excitable again and the wavefront can pass down A.

Thus, a re-entry wavefront has been formed that is constantly meeting excitable myocardium.

Triggered activity

This has features of both the above mechanisms. They are caused by spontaneous (hence automatic) *afterdepolarizations* (ADs) occurring late in phase 3 (*early ADs*) or in phase 4 (*delayed ADs*) of the action potential. These ADs, however, are often triggered by premature beats and are therefore inducible (like re-entry). If these ADs reach the threshold level, then a single or burst of action potentials is set off. The ADs can be induced experimentally by ischaemia, QT-prolonging drugs, cell injury, or low potassium. This mechanism underlies torsades de pointes and arrhythmias due to digoxin toxicity.

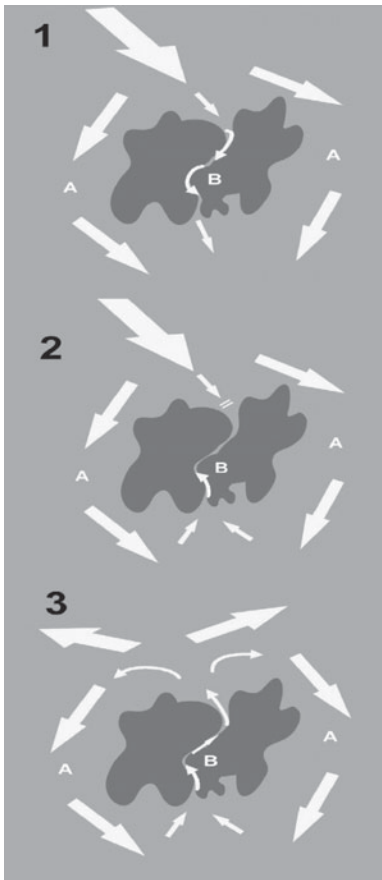


Fig. 11.1 Re-entry as a mechanism of tachycardia.

1. Normal sinus beat passing around and through scar
2. Ectopic beat passing around but blocked through scar
3. Re-entry circuit of tachycardia

(Dark grey represents scar, light grey normal myocardium, and white arrows electrical wavefronts.)

The electrophysiology study

The electrophysiology (EP) study is most useful for the diagnosis of tachycardia. When this has already been documented or is strongly suspected, then it is usually the first part of a combined procedure with catheter ablation to cure the arrhythmia. Note that in EP it is usual to discuss cycle lengths (in ms) rather than heart rates e.g. 60/min = 1000 ms, 100/min = 600 ms, 150/min = 400 ms.

Mapping electrical activity in the heart

EP is wrongly considered to be complex. Fundamentally, it is just recording of the heart's electrical signals either during sinus rhythm, arrhythmia, or in response to pacing at specific sites. The electrocardiogram (ECG) provides a great deal of this information and so a full 12-lead ECG is recorded throughout the procedure.

The intracardiac electrogram (ICegram)

The ECG summates the entire cardiac activation. By placing 2 mm electrodes directly on the heart's endocardial surface, the electrical activity at precise locations is known. The ICegram is therefore much narrower than the ECG and is best appreciated at a sweep speed of 100 m/ms, four times faster than a standard ECG recording.

The potential difference between either two closely spaced electrodes (a bipolar electrogram) or one electrode and infinity (a unipolar electrogram) can be recorded. The unipolar electrogram is more accurate regarding direction and location of electrical activity; however, it is subject to much greater interference. Note that a pacing current can be passed through any of these electrodes. Standard catheter location is shown in Fig. 11.2.

Pacing protocols

Pacing in the EP study is done in a predefined manner, termed *programmed stimulation*. This has three forms:

- *incremental pacing*: the pacing interval is started just below the sinus interval and lowered in 10 ms steps until block occurs or a predetermined lower limit (often 300 ms) is reached
- *extrastimulus pacing*: following a train of 8 paced beats at a fixed cycle length, a further paced beat (the extra stimulus) is introduced at a shorter coupling interval (the time between the last stimulus of the drive and the first extrastimulus). The stimuli of the drive train are conventionally termed S_1 , the first extra stimulus S_2 , the second extrastimulus S_3 , and so on. Extra stimuli can also be introduced after sensed heart beats ('sensed extras')
- *burst pacing*: pacing at a fixed cycle length for a predetermined time.

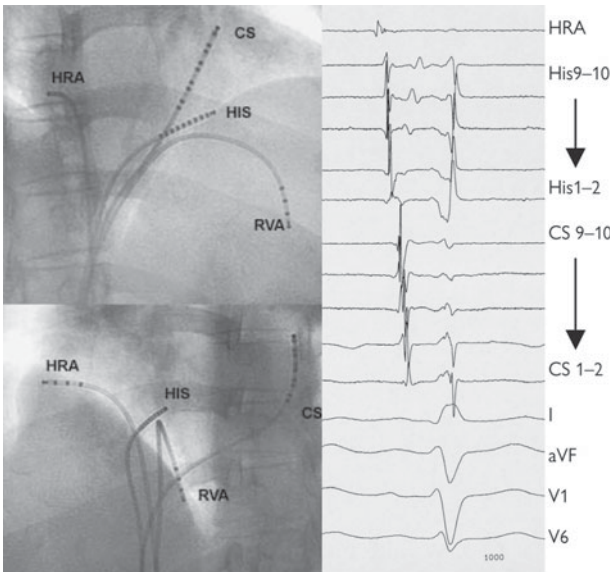


Fig. 11.2 Standard positions of catheters in the EP study and intracardiac electrograms at those sites. Catheters have been passed up into the right heart from sheaths in the femoral veins under fluoroscopic guidance. These images from the right anterior oblique (above) and left anterior oblique (below) demonstrate the standard positions at the high right atrium (HRA) close to the SAN, on the His bundle (HIS), at the RV apex (RVA) and a catheter passed through the os of the coronary sinus (CS), which wraps around the left posterior atrioventricular groove. From this position, ICeograms are recorded from the left atrium and ventricle. This catheter is often inserted via the left or right subclavian veins.

The ICeograms are conventionally ordered HRA, HIS, CS, and RV (not displayed here), with an ECG lead at the bottom. In SR then activation is seen to start at the HRA, pass across the His bundle, and then along the CS catheter proximally to distally. Earliest ventricular activation is at the RVA (where the Purkinje fibres insert).

Normal *sinus intervals* are PA = 25–55 ms, AH = 50–105 ms, HV 35–55 ms, QRS <120 ms, corrected QT <440 ms men, <460 ms women.

Uses of the electrophysiology study

Sinus node function

The *corrected sinus node recovery time* and *sinoatrial conduction time* are both measures of SAN function. Unfortunately, however, they are unreliable tests as SAN function is greatly influenced by autonomic tone, drugs and observer error. SAN dysfunction is best assessed with ambulatory monitoring and exercise testing. It is very rare that invasive EP testing would contribute to the decision to give a patient a permanent pacemaker and therefore it is not part of our routine procedure.

AV conduction

Heart block: The degree of heart block is assessed via the ECG, which can also indicate the level (i.e. either at the AV node itself or in the His Purkinje system, infra nodal). The level of block is ascertained easily in the EP study. The AH time is prolonged in nodal and the HV time in infranodal block. The AH (but not the HV) time may be shortened by exercise, isoprenaline or atropine and prolonged by vagal manoeuvres.

AV nodal function: This is assessed both anterogradely (A to V) and retrogradely (V to A), using both incremental and extrastimulus pacing. By incremental pacing at the HRA, conduction is observed in the His bundle and RVA until block occurs. The longest pacing interval at which block occurs is the anterograde Wenckebach cycle length (WCL). Normal values are <500 ms; however, this increases with age and autonomic influences. The retrograde WCL is also measured; however, absent VA conduction can be normal. From the HRA, extrastimulus pacing is performed. As the coupling interval between S_1 and S_2 is reduced, AV conduction is observed. The longest S_1 – S_2 interval at which AV block occurs is the anterograde atrioventricular node (AVN) effective refractory period (ERP). This is measured at drive trains of 600 and 400 ms. If VA conduction is present, the retrograde atrioventricular nodal effective refractory period (AVNERP) is measured.

Decremental conduction: This is the key physiological property of the AV node. As the interval between successive impulses passing through the AV node decreases, the conduction velocity within the AV node also decreases. In AV conduction, this is manifest as a prolongation of the AH (and AV) interval, as the atrial pacing interval decreases. This phenomenon can be observed during incremental and extrastimulus pacing. During extrastimulus pacing, if the AH interval is plotted against the S_1 – S_2 ($=A_1$ – A_2), then an anterograde conduction curve can be plotted.

Dual AV nodal physiology: It is possible in many patients (but not all) to identify two electrical connections between the atrial myocardium surrounding the compact AV node and the node itself, which have different conduction properties. The *slow pathway* has slower conduction velocity but a shorter ERP than the *fast pathway*. This is observed by plotting an anterograde conduction curve. For longer A_1 – A_2 intervals, AV conduction is preferentially via the fast pathway; however, once the fast-pathway ERP is reached, conduction is via the slow pathway and consequently the AH time suddenly prolongs. This is called an AH interval *jump* and is defined as a lengthening of the AH by >50 ms, following reduction in the A_1 – A_2 interval of 10 ms. Dual AV nodal pathways are the substrate for AVNRT.

Table 11.2 A standard basic electrophysiology study

Pacing protocol	Measure	Comments
1. Sinus rhythm	Basic sinus intervals (PA, AH, HV, QRS, corrected QT)	Is there AV conduction block?
2. Incremental ventricular pacing (IVP)	RWCL	Is VA conduction present? If so, is atrial activation normal and decremental?
3. Incremental atrial pacing (IAP)	AWCL	Is AV conduction decremental? Is pre-excitation manifest during pacing?
4. Extrastimulus pacing from atrium at 600 and 400 ms	Anterograde AVNERP at 600 and 400 ms	Is AV conduction decremental? Is pre-excitation manifest during pacing? Is there dual AV nodal physiology?
5. Extrastimulus pacing from ventricle at 600 and 400 ms	Retrograde AVNERP at 600 and 400 ms	Is VA conduction present? If so, is atrial activation normal and decremental?
6. Arrhythmia induction from atrium. Use 2–4 extrastimuli, sensed extra stimuli, burst pacing		Note pacing protocol that induces arrhythmia. Is it reproducible? Compare arrhythmia induced to clinical arrhythmia.
7. If VT suspected, perform Wellen's protocol	VERP at 600 and 400 ms	
8. Repeat steps 2–7 during isoprenaline infusion		Essential for tachycardias with enhanced automaticity mechanism.

AVNERP = atrioventricular nodal effective refractory period; AWCL = anterograde Wenckebach cycle length; RWCL = retrograde Wenckebach cycle length; VERP = ventricular effective refractory period.

Indications for electrophysiology study

- Diagnose the mechanism of documented symptomatic tachycardia (usually proceed immediately to ablation)
- Diagnose the mechanism of tachycardia in a patient with palpitations and suspected arrhythmia (may proceed immediately to ablation)
- Determine electrical properties of the accessory pathway (Wolff–Parkinson–White (WPW))—stratify the risk of sudden cardiac death (SCD) and need for ablation
- Risk stratification of SCD in patient with impaired left ventricular (LV) function or inherited arrhythmia, e.g. Brugada syndrome and need for implantable cardiac defibrillator (ICD)
- Diagnose the mechanism of syncope—when arrhythmia is strongly suspected
- Look for evidence of AV nodal conduction disease (measure HV interval) and need for pacemaker.

Identifying abnormal AV connections

In normal hearts there is only one connection between the atrium and ventricle, the AV node. Activation of the atrium (during V pacing) or ventricle (during A pacing or SR) should therefore start at the AV node. Accessory pathways (APs) do not decrement. Their presence can be identified by both abnormal activation patterns and conduction physiology using incremental and extrastimulus pacing.

Atrial pacing: As the AV node decrements, a greater proportion of ventricular activation will occur via the AP. Thus, non-decremental AV conduction times and broadening of the QRS complex will be observed as the pacing interval shortens. Note: If the ERP of the AP is shorter than the ERP of the AV node, then the QRS will suddenly narrow and the AV time suddenly prolong when the AP blocks.

Ventricular pacing: The normal order of atrial activation is His then CS (proximal to distal) and finally the HRA, termed *concentric* activation. If the atrium is activating via an AP, an *eccentric* activation pattern is observed. The site of the earliest atrial activation will localize the AP. Non-decremental VA conduction is also seen.

Induction of arrhythmia

The presence of an AP, dual AVN physiology or a known ventricular scar provides the substrate for a tachycardia but does not necessarily imply it will occur. A diagnosis can only be confirmed by inducing the tachycardia.

In addition to the pacing techniques described, burst pacing, extrastimulus pacing with multiple extrastimuli, and sensed extras are deployed. If this fails, pacing manoeuvres can be repeated during an isoprenaline infusion (1–4 mcg/min) or boluses (1–3 mcg). This is particularly important for tachycardias with an enhanced automaticity mechanism. 'Aggressive' induction protocols increase the likelihood of inducing an unwanted arrhythmia such as AF or VF (ventricular fibrillation).

Once a tachycardia is initiated, it is useful to compare it with a 12-lead ECG recorded during symptoms to ensure this is the clinical arrhythmia. How individual tachycardias are diagnosed and treated is considered in subsequent chapters.

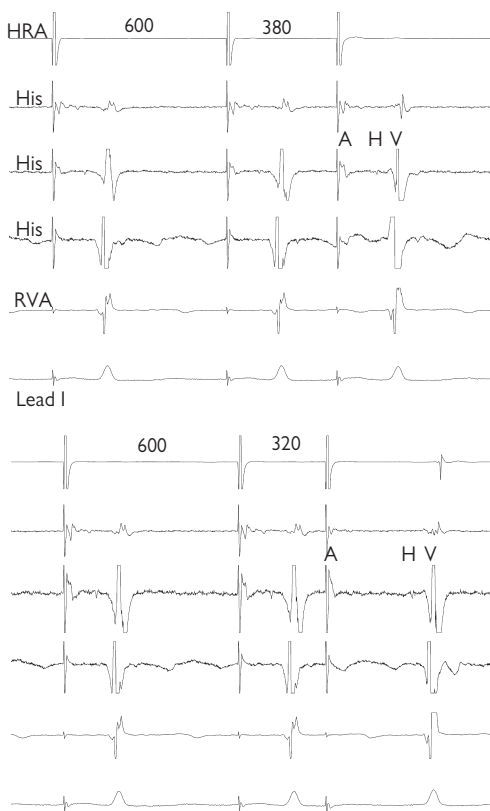


Fig. 11.3 AV nodal jump demonstrated during anterograde conduction curve. In both panels, 5 ICagrams are shown; top to bottom: high right atrium (HRA), 3 bipolar recordings from the bundle of His (His), right ventricular apex (RVA) and lead 1 of the ECG are displayed. 8 paced beats (drive train) have been delivered through the HRA at 600 ms and then a single extra stimulus. Only the final two beats of the drive train and the extra stimulus are shown. The coupling interval of the extra stimulus is 380 ms and 320 ms in the top and bottom panels respectively. Despite only a slight shortening of the coupling interval, there is dramatic lengthening of the AH (and AV) time, suggesting dual AVN physiology.

Programmed ventricular stimulation

An EP study focusing on induction of ventricular arrhythmias (the VT stimulation study) has previously been used to risk stratify for SCD, and to decide on the effectiveness of antiarrhythmic drugs in suppressing VT, and the need for an ICD. Evidence has now accumulated, however, that it is of little predictive value, and that decisions regarding ICD prescription should be based on other risk factors, particularly LV function. The EP study can be useful prior to ICD implant for other reasons:

- to aid programming of the device:
 - is VT well tolerated haemodynamically?
 - is it easily terminated with overdrive pacing?
 - is there VA conduction? During V pacing or VT?
- to assess suitability for VT ablation (e.g. bundle branch VT)
- are other arrhythmias present and easily induced?

Programmed ventricular stimulation is performed using the protocol devised by Wellen, or a modification thereof (see below).

Protocol for programmed ventricular stimulation

- From the RV apex, extrastimulus pacing, reduce the coupling interval until refractory:
 - 1 extrastimulus during SR
 - 2 extrastimuli during SR
 - 1 extrastimulus following 8 paced beats at 600 ms
 - 2 extrastimuli following 8 paced beats at 600 ms
 - 1 extrastimulus following 8 paced beats at 400 ms
 - 2 extrastimuli following 8 paced beats at 400 ms
 - 3 extrastimuli during SR
 - 2 extrastimuli following 8 paced beats at 600 ms
 - 3 extrastimuli following 8 paced beats at 400 ms
- If no ventricular arrhythmia is induced, repeat from RV outflow tract.

Thus, the pacing protocol becomes gradually more aggressive. The more aggressive the induction protocol, the less specific the result. The most useful result is induction of a sustained monomorphic VT with one or two extrastimuli. This indicates a potential substrate for ventricular arrhythmias. Non-sustained VT, polymorphic VT, and VF are all non-specific results.

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New technologies

Non-fluoroscopic three-dimensional mapping

EP procedures have become increasingly complex (e.g. ablation of AF or atrial tachycardia in congenital heart disease), leading to longer procedures with greater X-ray exposure. Non-fluoroscopic electroanatomical mapping systems help overcome these challenges by generating a three-dimensional (3D) image as the ablation catheter is moved around the cardiac chamber being mapped. Two systems are commonly used; *Carto* (Biosense Webster) and *Navx* (St Jude Medical), which locate the catheters using magnetic and electrical fields respectively.

These maps can be used as anatomical guides, and can display the timings (activation maps) or voltages of ICegrams represented by colours. The maps can be viewed in any orientation or from internally. Points of interest or labels, e.g. ablation lesions, can be marked, which gives memory of where the catheter has been. This is particularly useful in ablation of AF where a series of ablation points need to be delivered to from continuous circular or linear ablation lines. The identification of areas of scar (voltage mapping) is essential in VT ablation, as these are critical to its re-entrant mechanism.

Non-contact mapping (Ensite Array, St Jude Medical), allows simultaneous collection of ICegrams from the entire endocardial surface of the chamber in which the catheter is placed. An array of 64 unipolar electrodes, mounted on a balloon, records the signals from the endocardium conducted through the blood. The 'virtual' ICegrams are reconstructed and displayed on a map of the chamber. The mechanism of a regular tachycardia can be determined from a single ectopic beat.

Image integration (Fig. 11.4)

A computed tomography (CT) or magnetic resonance imaging (MRI) scan of the patient's thorax can be segmented to provide a 3D image of the patient's own LA (or other chamber). This is then registered with the mapping system (*Carto* or *NavX*) by moving the mapping catheter to at least four anatomical points (e.g. junction of a pulmonary vein and the LA) and simultaneously marking them on the image and mapping system. The reconstruction of the LA is then locked into the mapping system, so that the operator can navigate around the complex unique anatomy of a patient's LA without the need for X-ray.

Remote navigation of ablation catheters

Robotic technologies have been a great success in urological and cardiac surgery. In order to overcome difficulties with manual catheter manipulation in complex procedures, these have been applied in EP—with the operator seated in the lab control room rather than standing by the patient. Proposed advantages are: improved catheter stability and reach, better ablation lesion formation, and reduced operator X-ray exposure and fatigue, which may translate into better clinical outcomes.

Niobe (*Stereotaxis*) is a magnetic navigation system in which a low-intensity magnetic field is created by two large magnets permanently housed either side of the cathlab table. A purpose-built mapping catheter contains three magnets that align themselves within the magnetic field. Movement of the catheter is achieved by shifting the magnetic field around,

controlled by a computer mouse on a desktop. *Sensei* (Hansen Medical) is a robotic navigation system in which a steerable sheath is controlled by a robotic arm attached to the table. This responds to manipulation of a 3D joystick at a purpose-built workstation. The sheath can house any ablation catheter and therefore is compatible with any other mapping system.

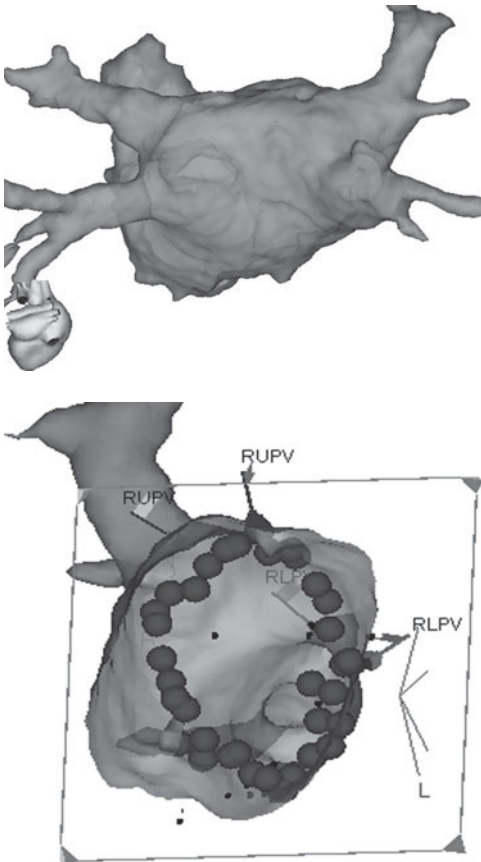


Fig. 11.4 Image integration. The top image of a LA from the PA perspective reconstructed from an MR scan of the heart taken pre-procedure. The image is registered with the 3D mapping system. The bottom image is the LA viewed from within at a left lateral projection so that the ablation lesions that have been delivered around the right pulmonary veins are visible.

Catheter ablation

In medical terms, ablation is the removal of tissue. As many tachycardias depend on discrete foci or pathways to be sustained, they are amenable to cure by destruction of these areas.

Energy sources for ablation

Radiofrequency (RF) energy

Cells are destroyed by heating $>50^{\circ}\text{C}$. The RF generator delivers an alternating current of 500–750 KHz between the active catheter electrode and a large indifferent electrode placed on the patient's skin. The ions within cells immediately adjacent to the catheter are agitated and generate heat (resistive heating). The heating power generated in this way dramatically decreases as the distance from the catheter increases. The remaining heat is conducted away to the surrounding tissue. A lesion of ~ 5 mm depth is formed after 30–60 s, which is sufficient to destroy the full thickness of atrial myocardium. Catheters are 7 Fr, with tip electrodes of 4 mm length as standard or 8 mm where longer lesions are needed.

If the temperature approaches 100°C , boiling of cell water occurs, generating steam that escapes either by exploding through the endocardium causing a large lesion (cavitation) or through the pericardium (perforation \pm tamponade). Temperature is monitored at the tip of the catheter, and power delivery is automatically limited to prevent such overheating. The generator allows the power, temperature, and duration of each RF delivery to be adjusted.

Irrigated RF

The tip of the catheter is cooled during RF by the flow of blood, so the hottest part of an RF lesion is 1 mm beneath the surface. Stasis of flow occurs as the lesion is formed; hence the temperature rises, limiting the amount of power that is delivered and therefore size of the lesion. Heparinized saline, passed through a multiple lumen in the tip of the catheter at a rate of 10–30 ml/h, continuously cools the catheter allowing higher powers and larger lesions to be formed. This is needed where the myocardium is thick, e.g. left ventricle (VT) or Eustachian ridge (typical atrial flutter). Low-flow (2 ml/h) RF ablation is useful to keep the tip of the catheter free of thrombus, reducing stroke risk during RF in the LA or LV.

Cryoablation

Completely contained within the specialized ablation catheter, liquid nitrous oxide released into the tip rapidly vaporizes and removes heat from the tissue in contact with the catheter. The gas is rapidly recycled back to the catheter console. The tissue temperature (monitored at the tip of the catheter) falls to -30°C , at which stage there is reversible loss of cell function. If an appropriate response is seen (e.g. loss of pre-excitation during AP ablation,) then the tissue is further cooled to -70°C for 4 minutes to cause permanent destruction. The ice formed adheres the catheter to the tissue, making it very stable. If, however, an adverse change is seen (e.g. AVN block) at -30°C , then the tissue can be rewarmed, theoretically without permanent damage.

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Complications of catheter ablation

The general complications associated with ablation are described here. The overall major complication rate for ablation of SVT is <1% and for complex arrhythmia (AF, VT) 3%. Specific issues in AF ablation are discussed later.

Major complications

- *Death* (<0.1%)
- *Bleeding*: generally only venous access is used, so major vascular damage requiring surgery is rare. This may be exacerbated by procedural use of heparin or warfarin. Haematoma can be due to persistent arterial or venous bleeding, arteriovenous fistula, or pseudoaneurysm. Large local or retroperitoneal haematoma may require transfusion. Compression and reversal of anticoagulation with protamine, recombinant factor VIII (or fresh frozen plasma (FFP)) and vitamin K may be needed. Ultrasound and contrast CT (CT angio) are used to diagnose the cause and extent of bleeding
- *Stroke* (<0.2% for supraventricular tachycardia (SVT)): the risk is higher for left-sided procedures or where cardioversion to SR from AF or flutter occurs. Minimize risk by: preoperative transoesophageal echocardiography (TOE), intraoperative heparin guided by activated clotting time (ACT), postoperative anticoagulation (aspirin or warfarin), irrigated catheters, continuous pressured heparinized saline administration through left-sided sheaths, cryoablation
- *Cardiac tamponade* (<0.2% for SVT): the risk is higher if trans-septal puncture is performed, but can occur even during diagnostic procedures. Blood pressure (BP) is monitored throughout the procedure, and in any hypotensive episode tamponade is suspected. The EP lab should be equipped with a hand-held ECHO machine and emergency pericardial aspiration sets. Doctors performing trans-septal punctures need to be experts in pericardial aspiration
- *AV nodal block* (<1% for SVT): high risk for septal AP or AVNRT (slow pathway) ablation. During RF, continuously image the catheter position and atrial and ventricular electrograms. If AV, VA block, or catheter movement occurs, **STOP**. Cryoablation may be preferred for high-risk cases
- *Deep vein thrombosis (DVT) and pulmonary embolism (PE)*: due to placement of multiple catheters in small veins for prolonged periods. If patients have a tendency to thrombosis, use heparin and continuous irrigation of sheaths
- *Coronary artery spasm/MI*: transient ST elevation and chest pain may occur without any long-term effect due to spasm
- *Pneumothorax*: only if a subclavian approach is used for catheters (coronary sinus)
- *X-ray exposure*: EP cases may be prolonged. Deterministic effects such as skin damage can be avoided with care to fluoroscopy technique. Women of fertile age should be counselled and have pregnancy tests if necessary. Non-fluoroscopic catheter location (Carto, NavX) is increasing

Minor complications

These are common. Liberal use of local anaesthetic and conscious sedation (combined opiates and benzodiazepines administered IV) can prevent these.

- *Chest pain*: occurs transiently during energy delivery
- *Vasovagal episode*: often occurs during initial percutaneous sheath insertion; ensure the patient has an IV cannula before entering the lab
- *Groin pain, bruising, or haematoma*: common at puncture site, particularly if anticoagulation is used.

Trans-septal puncture

This permits a direct route to the LA via the intra-atrial septum and systemic venous system. Previously, the technique was used infrequently by cardiologists for mitral valvuloplasty; however, due to the massive expansion in ablation of AF, it is now a routine skill of the modern cardiac electrophysiologist. A detailed description of the technique is available.¹

Electrophysiology (catheter ablation) indications

- AF
- Left atrial tachycardia
- VT
- Left-sided accessory pathways.

Other indications

- Percutaneous mitral valvuloplasty
- Haemodynamic study of the left heart with prosthetic AV present.

Technique (see Fig. 11.5)

This is described using a Brockenbrough needle and Mullin's sheath/dilator set. Other needles and sheaths are available.

- *Preparation:* if TOE is performed, review the anatomy of the RA, LA, and intra-atrial septum. Optimal patient preparation—fasted but well hydrated, IV cannula, etc.
- *Percutaneous access* using Seldinger technique via right femoral vein for trans-septal sheaths and access for other catheters. Trans-septal sheaths and dilator are delivered to the SVC over a long guide wire. The needle has a lumen to allow pressure monitoring. This is passed up the dilator but kept just within the tip of the sheath. An EP catheter is positioned on the His or in the coronary sinus, as an anatomical marker.
- *Trans-septal puncture:* the needle and sheath are held together, with the handle pointing toward 4 o'clock. The entire rig is pulled inferiorly while screening in LAO (left anterior oblique) projection, until the tip of the catheter and needle are seen to 'jump' medially as it falls from the SVC to the RA, and then a more subtle jump as it falls into the fossa ovalis. The position is imaged in right anterior oblique (RAO) projection, to ensure it is posterior to the aortic root. The needle is then advanced through the septum to the LA. The pressure wave changes to LA trace. The dilator and sheath are advanced over the needle into the LA.
- *Monitoring:* the dilator and needle are removed to leave the sheath in the LA as access for EP catheters. Pressurized heparin saline flush is attached to the sheath. Heparin is given in boluses to keep the ACT over 300 s, while the catheters are in the left heart.

¹ Earley MJ (2009). How to perform a transseptal puncture. *Heart* **95**: 85–92.

Complications

Occur in <1% of cases:

- pericardial effusion or tamponade
- aortic root needle puncture
- right or left atrial wall needle puncture
- pleuritic chest pain
- stroke/transient ischaemic attack (TIA)
- transient ST elevation of inferior leads
- persistence of atrial septal defect (ASD).

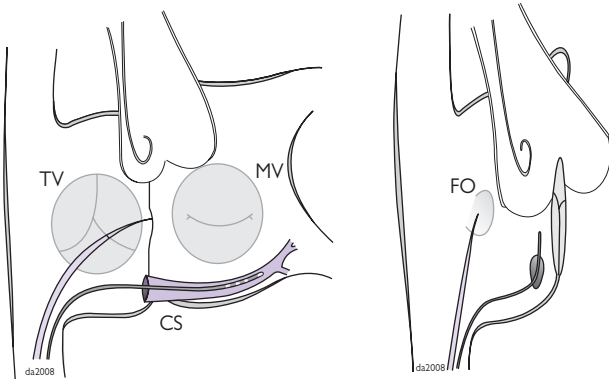


Fig. 11.5 A diagram showing the position of the trans-septal needle optimally positioned in the fossa ovalis (FO) ready for puncture through into the left atrium, on the left, LAO projection; right, RAO projection. The most important structure to avoid is the aortic root, in which a pigtail catheter can be sited to visualize it. Alternatively, a catheter marking the os of the coronary sinus (CS) or the bundle of His (not shown) can be used. TV = tricuspid valve; MV = mitral valve.

Atrial arrhythmias: mechanism

There are only two main types of atrial arrhythmias: atrial tachycardia and atrial fibrillation. Atrial tachycardia is characterized by repetitive single electrical wavefronts following the same course, causing regular atrial activation. The source of these wavefronts can either be focal or a re-entry circuit. AF is characterized by multiple wavefronts following chaotic, constantly varying, courses.

Focal atrial tachycardia

Atrial cells with enhanced automaticity fire more quickly than the SAN. Any atrial cells can do this, but common foci are the crista terminalis, PV–LA junction, vena cavae–RA junction, and triangle of Koch. It is possible for re-entrant circuits to form within a very small group of cells, termed 'micro-re-entrant'; however, distinguishing this from a focal mechanism is very difficult even at EP study.

Macro-re-entrant atrial tachycardia

This is due to a re-entrant circuit bordered by areas of fixed conduction block—either anatomical barriers (e.g. valve annulus) or areas of scar. The commonest form is *typical atrial flutter*, where the circuit is contained within the RA, rotating anticlockwise around the tricuspid valve (see Fig. 11.6). The opposite (clockwise) of this is *reverse typical flutter*. Any other macro-re-entrant atrial tachycardia in the right or left atrium can be termed *atypical atrial flutter*. Most atypical circuits are around areas of scar, most commonly due to catheter ablation of AF, cardiac surgery, or congenital heart disease. These circuits need to be carefully mapped before ablation can be performed. The term *flutter* is an ECG diagnosis, i.e. P-wave rate >240/min.

Atrial fibrillation

The mechanism underlying the chaotic electrical wavefronts that characterize AF is both focal and re-entry. Paroxysmal AF usually has a focal mechanism, and persistent AF is due to multiple re-entry wavefronts.

Focal: Wavefronts from a single source emerge from either cells of enhanced automaticity (like focal atrial tachycardia) or a single small re-entry circuit (micro-re-entrant). The pulmonary veins are the source of these wavefronts in >80% of cases. The wavefronts are of such a high frequency that the rest of the atrial myocardium cannot conduct them uniformly. This causes them to break up to give multiple wavefronts (= fibrillatory conduction, Fig. 11.6). This is usually the mechanism of paroxysmal AF and these foci are considered triggers of AF.

Multiple re-entry: 4–6 separate re-entry circuits of constantly varying course and velocity rotate around the atria, colliding with each other and anatomical structures such as veins and valves. They are self-perpetuating. The larger the atria, the more room these wavefronts have to rotate and the more likely it is that they will be sustained.

Remodelling: This is a key concept in understanding the mechanism of AF. Episodes of AF, no matter how short, will alter the electrical properties of the myocytes due to downregulation of calcium channels and shortening

of action potential duration (electrical remodelling). This makes it easier for the myocardium to support re-entry wavefronts. Thus, after multiple paroxysms, AF may become sustained, i.e. persistent. After months of AF, the atria will become dilated and fibrosis will occur (structural remodelling), further promoting re-entry. Remodelling explains the untreated natural history of AF to progress from paroxysmal to persistent to permanent. This is the pathophysiological explanation of the phrase 'AF begets AF'.

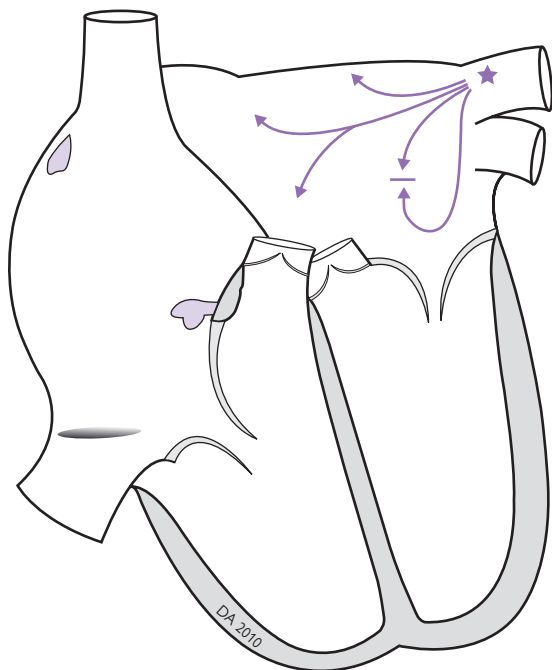


Fig.11.6 Cartoon depicting AF being driven by the source of electrical wavefronts emerging from the left superior pulmonary vein (star). The arrows represent electrical wavefronts breaking up to give multiple wavefronts—the hallmark of AF. Electrical isolation of this vein by ablation will prevent future episodes.

Ablation of atrial tachycardias

Focal atrial tachycardia (FAT)

- Tachycardia must be induced and sustained to map the location in the atria of earliest activation (the focus) and this may need an isoprenaline infusion.
- The hallmark of atrial tachycardia is dissociation of the atrial electrograms from ventricular during tachycardia. This may occur spontaneously (AV block), or it may be necessary to pace the ventricle faster than the atrium.
- The morphology of P waves on ECG may be used to identify the location of the source. (+ve I and aVL, -ve V₁ = high lateral RA; -ve II, III and aVF = LA or RA posteroseptal; +ve I, aVL and V₁ = right PVs; -ve I and aVL, +ve V₁ = left PVs,). Detailed algorithms are available.¹
- Catheters in the RA and CS will identify whether the LA or RA activates first. Beware: FAT from the right superior pulmonary vein (RSPV) may give the appearance of having an RA origin. The RA is easily mapped with an ablation catheter via the inferior vena cava (IVC), but the LA requires a trans-septal puncture.
- A successful site usually has a local electrogram at least 30 ms ahead of the P wave.
- Success rates are >90%.

Typical atrial flutter

- The re-entry circuit can be interrupted by creating a series of ablation lesions adjacent to one another so that a line of conduction block is created between the IVC and tricuspid valve (see Fig. 11.7). This is therefore a purely anatomical procedure that can be performed in SR or tachycardia.
- Patients in atrial flutter will need perioperative anticoagulation with warfarin.
- Commonly, the tricuspid valve (TV) annulus is mapped with a 20-pole catheter, but this is not necessary.
- Success is proved by termination of tachycardia (if present) and demonstrating conduction block in both directions across the RA isthmus (bidirectional block).
- Acute success occurs in 90% of cases, with a 10% relapse.
- 30% of patients who undergo atrial flutter ablation later develop AF.

¹ Kistler PM, Roberts-Thomson KC, Haqqani HM, et al (2006). P-wave morphology in focal atrial tachycardia: development of an algorithm to predict the anatomic site of origin. *J Am Coll Cardiol* 48: 1010–17.

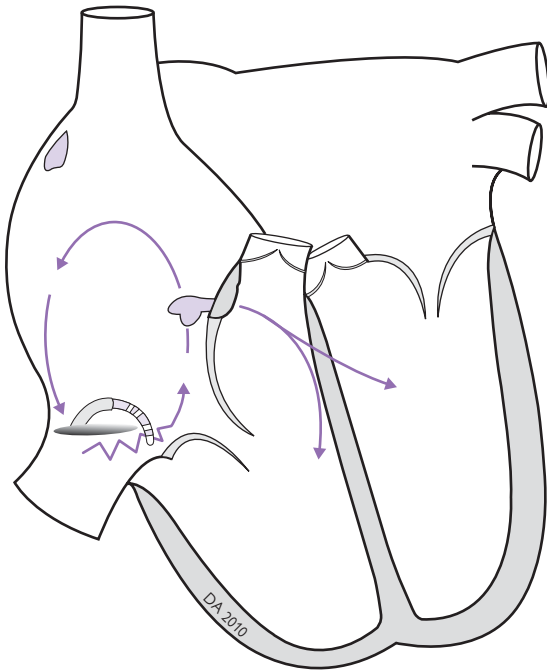



Fig. 11.7 Ablation of typical atrial flutter. The arrows represent the re-entry circuit activating around the RA with the critical isthmus of slowed conduction (zig-zag arrow) between the inferior vena cava (IVC) and tricuspid valve (TV). An ablation catheter is passed up from the IVC, and a series of ablation lesions delivered to join the TV to the IVC with a line of scar. In this way, no activation can pass through, and the re-entry circuit of typical atrial flutter is broken.

Catheter ablation of atrial fibrillation

This is now the 'bread and butter' of modern interventional EP practice. For paroxysmal AF, the strategy is to electrically isolate the PV, hence preventing triggering of these episodes. Ablation of persistent AF starts with PV isolation and is followed by more extensive ablation in the left and right atrium aimed at modifying the atrial myocardial substrate so that it cannot support the re-entry waves that sustain AF. High-volume EP units expect a success rate of >90% and >80% for paroxysmal and persistent AF, although multiple procedures may be required.

Patient preparation

The indication for ablation is symptomatic AF despite antiarrhythmic drugs. Patients need to be counselled of the 3% risk of a major complication, long procedure time (up to 4 hours), and need for multiple procedures. A TOE is usually performed to ensure the left atrium (LA) and left atrial appendage (LAA) are free of thrombus and to view the intra-atrial septum. A CT or MRI of the thorax may be performed to provide a LA reconstruction for image integration. A 3D mapping system is used (see  p. 556). Generally, the procedure is performed under local anaesthetic, with conscious sedation by a combination of opiates and benzodiazepines. Percutaneous access is via the femoral veins. Heparin is administered to maintain an ACT between 300 and 400s.

Pulmonary vein isolation

Trans-septal punctures are performed to deliver an irrigated RF ablation and circular PV mapping catheter to the LA. There are two methods for isolating the PVs using RF energy. *Segmental ostial isolation* selectively ablates the individual electrical connections between the LA and each PV until the electrical signals disappear in the vein. In *wide area circumferential ablation*, a continuous line of lesions is delivered well outside the PV, to form a circle that encloses an ipsilateral pair of PVs (Fig. 11.8). Regardless of technique, the end-point is that the electrical signals in the PV disappear. It is also possible to isolate the SVC and coronary sinus if there are triggers of AF present here.

New tools are available to deliver a 'one shot' ablation lesion that can isolate a PV. The most widely tested is the *cryoballoon* that delivers cryoablation via a balloon inflated in the LA and advanced into each PV over a guide wire. Clinical results are similar to conventional techniques but a higher incidence of phrenic palsy has been observed.

Substrate modification

Multiple strategies are adopted to achieve this. A *catheter maze* is when the LA and RA are compartmentalized by creating long lines of ablation within them to interrupt the multiple re-entry circuits. Common lines are; LA roof (from the left (LSPV) to the right superior pulmonary vein (RSPV)), mitral isthmus (left inferior pulmonary vein (LIPV) to the mitral valve (MV) annulus), CS roof (LA septum to LIPV along the posterior MV annulus), intercaval (SVC to IVC along the lateral RA), RA isthmus (TV to IVC), within the CS. In addition, *complex and fractionated atrial electrograms (CFAEs)* are ablated. These signals have high-frequency components and little isoelectric baseline. Several hypotheses exist as

to their genesis: turning or collision points for wavefronts, spiral rotas that drive AF, or autonomic nerve ganglia. Regardless of their cause, their ablation slows and terminates AF.

AF may organize into a regular *atrial tachycardia*. This is usually a macro-re-entrant mechanism and the circuit is defined by a combination of activation mapping with a 3D system and entrainment. Ablation is delivered to interrupt this. A common circuit runs around the MV and this can be interrupted by a line of ablation between the MV and LIPV.

If sinus rhythm is not restored by ablation alone, electrical cardioversion is performed. A final check is made of PV isolation, and the integrity of lines of block created.

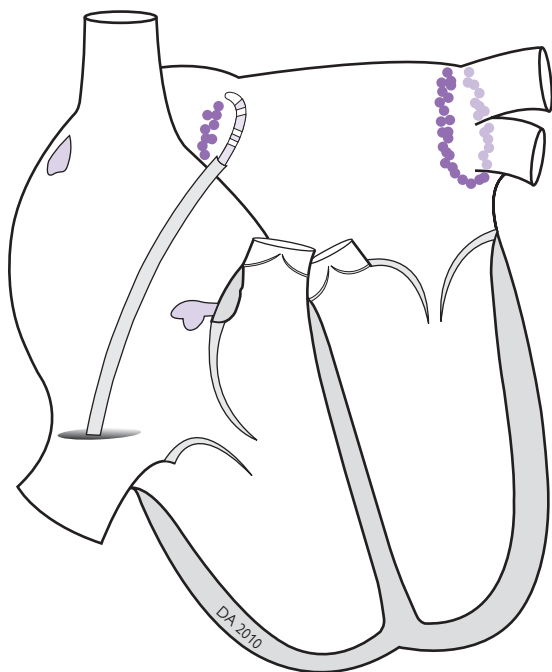


Fig. 11.8 Cartoon depicting pulmonary vein isolation by wide area circumferential ablation. A catheter is delivered to the left atrium via a trans-septal puncture. Ablation lesions have been delivered point by point to create a continuous line around the left superior and inferior PV together. The catheter is seen delivering lesions around the right PVs.

Complications of AF ablation

The risk exceeds that of standard SVT, with immediate procedural major complications occurring in 3%.

- *Bleeding*: groin complications are higher risk due to procedural use of heparin and/or warfarin
- *Stroke/TIA* (1%): risk higher due to extensive ablation in LA
- *Cardiac tamponade* (2%): the most frequent major problem due to a hole created during ablation. Small pericardial effusions may need no treatment but tamponade requires pericardiocentesis and reversal of anticoagulation. An ECHO is mandatory if there is any episode of hypotension in the postoperative period
- *Pulmonary vein stenosis*: this is now unusual as ablation is performed at the atrial aspect of the PV. To give symptoms, ≥ 1 PV needs to be severely narrowed ($>75\%$) or occluded. It presents insidiously with progressive dyspnoea, fatigue, cough, haemoptysis, and recurrent chest infections. Investigate by contrast CT, MR and ventilation–perfusion (V/Q) scan. Angioplasty can be performed
- *Atrio-oesophageal fistula*: a rare but usually fatal complication caused by ablation through the posterior LA. Great caution should be taken when ablating in this area (low power, short RF times)
- *Phrenic nerve palsy*: the course of the right phrenic nerve makes it vulnerable to damage during ablation of the lateral RA or right PVs. Paralysis of the right hemidiaphragm can occur; however, there is almost always full recovery within a few months, with long-term problems being unusual
- *Atrial tachycardia* occurs in 10–40% of patients within 3 months; persistent $>$ paroxysmal. This may cause much worse symptoms than AF, as the ventricular rate is faster and more difficult to control. Cardioversion, antiarrhythmic drugs, AV nodal blocking drugs can be used as a temporizing measure but further ablation is often needed.

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Mechanism of AV re-entry tachycardias

In young patients with paroxysmal regular narrow complex tachycardia, the diagnosis is either atrioventricular node re-entrant tachycardia (AVNRT) or atrioventricular re-entrant tachycardia (AVRT). The mechanism of both is re-entry (see Fig. 11.10, p. 575). The substrate for AVNRT is dual AVN pathways, and for AVRT the presence of an AP. Occasionally an atrial tachycardia may give an identical ECG appearance.

Diagnostic testing

Four standard catheters are positioned (see Fig. 11.2) and an EPS carried out (see Table 11.2, p.551). Look for evidence of dual AVN physiology and presence of an AP. If tachycardia is induced, atrial activation is observed to see whether it is via the AVN (AVNRT) or an AP (AVRT). Look closely for AVN block, BB block, and at the onset and termination of tachycardia. His synchronous ventricular premature beats (HSVPBs) are introduced to identify whether an AP is mediating the tachycardia (AVRT).

AV block

If AVN block occurs, but tachycardia persists, it is almost always an atrial tachycardia.

Onset

- AVN jump immediately followed by tachycardia: AVNRT.
- Loss of pre-excitation followed by tachycardia: AVRT.

Termination

- Last tachycardia complex atrial (block in AVN): AVNRT or AVRT (almost certainly not atrial tachycardia).
- Last tachycardia complex ventricular: atrial tachycardia (AVNRT or AVRT still possible).

His synchronous ventricular premature beats

The aim is to introduce a ventricular paced beat exactly coincidental with the His potential during tachycardia, to see whether the ventricle is an essential component of the re-entry circuit (Fig. 11.8). To do this the cycle length of the tachycardia is measured and a single sensed extrastimulus is delivered from the catheter in the RV at 20 ms less than the cycle length. This is repeated, reducing the coupling interval by 10 ms each time, until it is clear the sensed extra is pre-His. Tachycardia is then terminated and the electrograms analysed.

Analysis (Fig. 11.9): the HH and AA intervals are measured to ensure a stable tachycardia. The paced VPB must be synchronous with the His potential. The AA interval before and after the HSVPB are measured. If the subsequent A is premature, this implies that the atrium *must* have been activated via an AP (as we know the His bundle is refractory due the presence of the potential) and that the ventricle is part of the re-entry circuit hence AVRT. If the A is not advanced it suggests this is AVNRT.

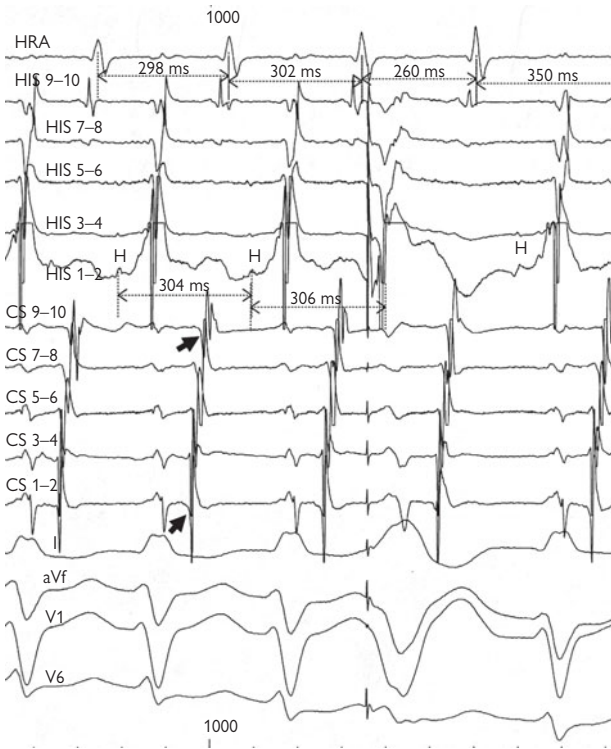



Fig. 11.9 HSPVBs resetting tachycardia. From top to bottom; intracardiac electrograms from high right atrium, His bundle catheter (proximal to distal), CS catheter (proximal to distal), and 4 surface ECG leads. The tachycardia cycle length is approximately 300 ms. During tachycardia the earliest atrial activation is at the distal coronary sinus (lateral left atrium)—see arrows. A sensed extra (the HSPVB) is introduced just ahead of the His potential (H). The next atrial complex is advanced (see cycle lengths measured at the HRA). This strongly suggests an AVRT mediated by a left lateral pathway.

Ablation of AV re-entry tachycardias

AVRT

Ablation must be performed during ventricular pacing or AVRT to identify the location of the AP (unless it is manifest on the resting ECG i.e. WPW). The earliest atrial activation is looked for with an almost continuous V then A electrogram. Its general location is found by bracketing it with a diagnostic catheter on the valve annulus, i.e. the CS catheter on the left side or a multipolar catheter on the right side. The precise location is then found with the ablation catheter. A true annular site is needed for success, so an equal-sized atrial and ventricular component on the mapping catheter is looked for. Left-sided APs are approached either retrogradely (via the aortic valve and LV) or anterogradely (trans-septal puncture).

AVNRT

The target is the slow AVN pathway (see  Fig. 10.9, p. 499). This is found inferior to the His bundle, close to the mouth of the CS. The presence of a slow pathway signal (bump and spike) with a small A and large V component should be seen. Energy is delivered, and usually transient slow junctional escape beats are seen as the cells die. If the catheter moves or any AV or VA block occurs, ablation is stopped immediately. If the lesion is therapeutic, a full EP study is then repeated to test and ensure no AVN damage. A successful procedural outcome is the inability to induce tachycardia, and complete loss of dual AV nodal physiology. Conventionally, the presence of a jump and a single ECHO beat is permitted, providing tachycardia cannot be induced. If isoprenaline was needed to induce tachycardia, it must also be used during testing.

Following ablation, full EP testing is repeated. VA conduction should be absent or via the AVN (concentric). If VA conduction persists, adenosine boluses are given to demonstrate both VA and AV block.

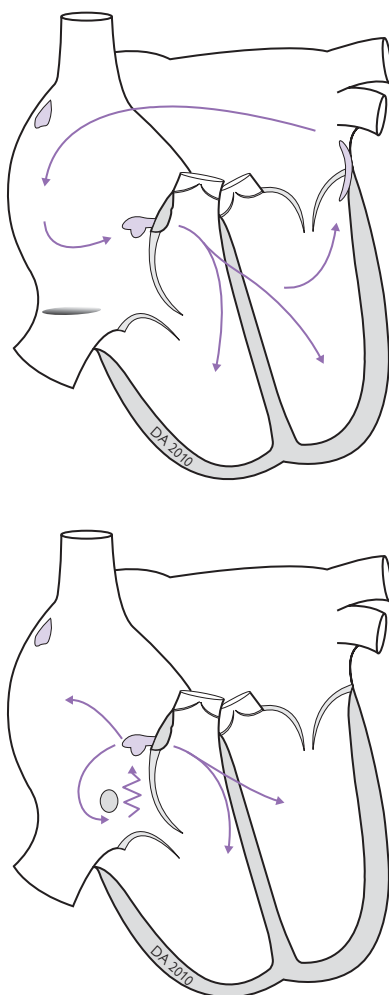


Fig. 11.10 Cartoon exhibiting mechanisms of SVT. Wavefronts depicted by arrows. Orthodromic AVRT (top panel) via a left-sided accessory pathway (AP). Activation from A to V is down the atrioventricular node (AVN), then across the ventricular myocardium and back from V to A up the AP, thus completing the circuit. The ventricle therefore is an essential part of the circuit. Antidromic AVRT (not shown) would activate in the opposite direction. Typical AVNRT (bottom panel) activates from the atrium to the AVN via the slow pathway (zig-zag arrow) and from the AVN to the atrium via the fast pathway (FP), thus completing the circuit. The ventricle is activated as a bystander via the bundle of His and is not an essential part of the circuit.

Accessory pathways (Wolff–Parkinson–White syndrome)

Definitions and ECG

The atria and ventricles are separated by the fibrous annuli of the TV on the right and MV on the left. The AV node is the only electrical connection in normal hearts. Abnormal accessory pathways can occur at any position along these annuli and are named accordingly (see Fig. 11.11). They may conduct in one or both directions. They are the substrate for AVRT to occur.

If an AP conducts anterogradely (A to V), it will be manifest on the ECG as pre-excitation (short PR interval and delta wave). The morphology of the delta wave predicts the location of the accessory pathway. An AP that conducts only retrogradely is described as concealed.

Wolff–Parkinson–White (WPW) syndrome strictly refers to APs that are both manifest as pre-excitation on the resting ECG and cause tachycardia.

Tachycardias

An AP can be associated with tachycardia by several mechanisms:

- *orthodromic AVRT* (commonest, accounts for 95% of AP mediated tachycardias)—narrow complex tachycardia
- *antidromic AVRT*—broad complex tachycardia
- *bystander*—SVT of another aetiology that conducts down the AP.

Prognosis

AF in the presence of an AP can be dangerous, as the ventricle is not protected by the decremental behaviour of the AV node. This can precipitate VF and sudden death. If patients are discovered incidentally, and are truly asymptomatic, then sudden death is extremely rare (between 1 in 2000 and 1 in 20 000 per annum). Invasive EP can be used to risk stratify patients.

A worse prognosis is predicted by:

- invasive EP testing:
 - anterograde ERP of the AP <250 ms (the longest interval that will not conduct down the AP during atrial extrastimulus pacing or AF)
 - inducible AVRT
 - multiple APs
- symptomatic tachycardia
- Ebstein's anomaly.

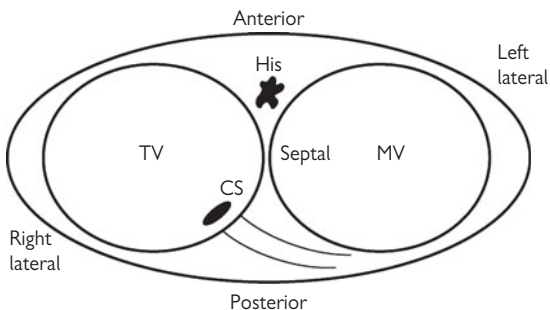


Fig. 11.11 Tricuspid (TV) and mitral valve (MV) annuli. Accessory pathways can be positioned anywhere on the annuli. They are named anatomically, i.e. anterior, left anterolateral, left lateral, left posterolateral, etc. Anteroseptal pathways are close to the His bundle and AV node and are termed parahisian.

Accessory pathways: localization

See Fig. 11.12.

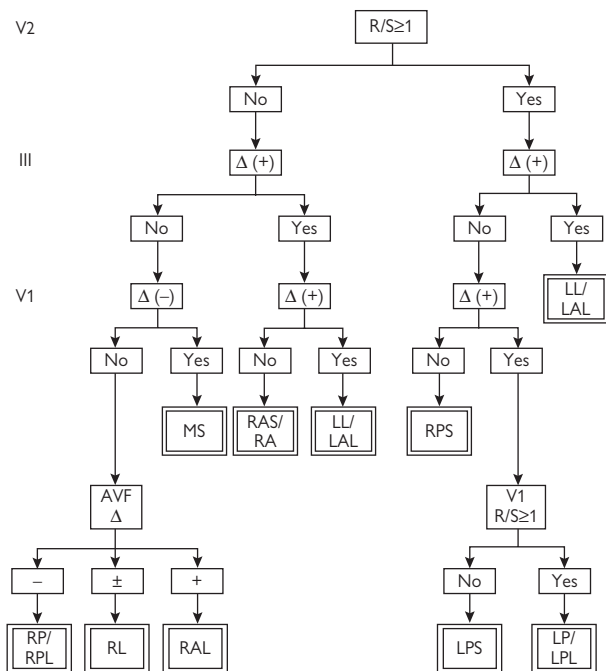


Fig. 11.12 Algorithm to locate the accessory pathway from the ECG with pre-excitation. γ = delta wave; reprinted from Chiang *et al* (1995). *Am J Cardiol* **76**(1): 40–6, with permission.

Accessory pathways: management

Ablation

APs can be cured by catheter ablation, and this is first-line treatment for symptomatic patients. A catheter is moved around the MV or TV annulus until the AP is located by finding the exact point of:

- earliest ventricular activation during SR or atrial pacing
- earliest atrial activation during ventricular pacing
- earliest atrial activation during orthodromic AVRT.

Acute success is >90%. The complication rate is very low (death 0–0.2%, AV nodal block <1%). For parahisian AP, the risk of AV nodal block is higher and cryoablation used if available. Left-sided pathways can be approached via the femoral artery, aorta, and left ventricle, or from the RA by a trans-septal puncture.

All symptomatic patients (with tachycardias) should be offered ablation. Asymptomatic young patients (<35 years) or those in a high-risk profession (pilots, divers, etc.) should be considered for invasive EP testing and ablation. However, the risk of sudden death must be balanced against the 2% serious complication rate of ablating the pathway (particularly if left sided or parahisian).

Pharmacological

Flecainide and propafenone slow conduction in the AP without affecting the AV node, and are the preferred agents. Drugs that slow AV nodal conduction only (verapamil and digoxin) should not be used unless invasive EP has demonstrated that the AP does not conduct anterogradely (or conducts only very slowly).


Unusual pathways

Mahaim pathways: These are APs between the RA and RV (atrioventricular) or RA and right bundle branch (atriofascicular). Unlike ordinary APs, they exhibit AV nodal properties of decremental conduction and sensitivity to adenosine. They only conduct anterogradely and mediate an AVRT with a broad complex left bundle branch block (LBBB) appearance. They are successfully treated by catheter ablation.

Mechanism of ventricular tachycardia

The improved survival from MI and widespread use of ICDs has led to a much greater need for invasive management of VT, i.e. ablation. In structural heart disease, VT almost always has a re-entry mechanism. Normal heart VT may be focal or re-entry.

Structural heart disease (see Fig. 11.13)

Scarred ventricular myocardium (due to infarction, cardiomyopathy etc.) provides the substrate for re-entry as described previously (see  p. 524). Scar acts as a barrier to conduction (fixed block); however, damaged but viable myocardium will provide areas of slow conduction, which are critical to allow re-entry circuits to form. This acts as a source of wavefronts that repeatedly depolarize the rest of the ventricle—hence monomorphic VT. LV scarring is much more common than RV other than in ARVC. A stable re-entry circuit can break down into chaotic activation, i.e. VF, hence the link between VT and sudden death. *Bundle branch VT* occurs in severely impaired ventricles, with damage to the conducting system and usually pre-existing bundle branch block. It is due to a re-entry circuit involving the right and left bundles.

Normal heart VT

RV (and LV) outflow tract VT has a focal mechanism with cells exhibiting enhanced automaticity. *Fascicular VT* is probably a re-entry circuit within either the posterior (usually) or anterior (rare) hemifascicles of the left bundle.

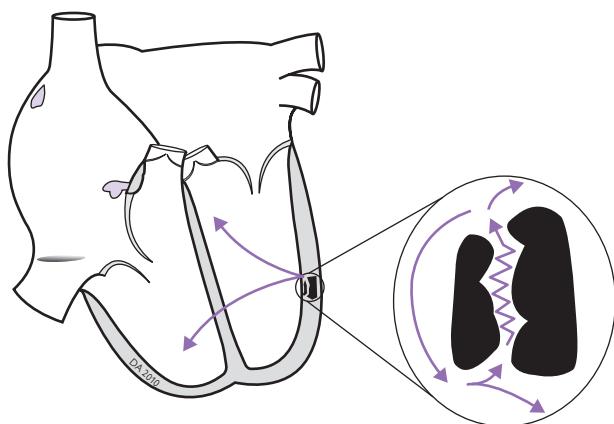


Fig. 11.13 Mechanism of VT in structural heart disease, e.g. post-MI. An area of scar in the LV myocardium (black) provides fixed conduction block. Electrical wavefronts (arrows) rotate around and slowly through the scar to form a re-entry circuit. This acts as a source of wavefronts to the rest of the ventricle. The area of slow conduction (zig-zag arrows) is termed the diastolic pathway as it activates during ventricular diastole. During VT, intracardiac electrograms recorded here time with the midpoint between successive QRS complexes. This is the target for ablation of VT.

Ablation of ventricular tachycardia

Clinical indications

- Recurrent symptomatic paroxysms of VT
- To reduce the number of therapies delivered by an automated ICD (AICD)
- Incessant VT

Activation mapping VT (see Fig. 11.14)

To successfully map the re-entry circuit, the patient must be in VT and therefore it needs to be haemodynamically well tolerated. Remote defibrillation paddles are attached to the patient so that if VF or hypotensive VT occurs, it can be immediately cardioverted.

If feasible, the LV is accessed both retrogradely via the femoral artery and aortic valve and anterogradely via the femoral vein and a trans-septal puncture. Using a 3D mapping system, the ablation catheter is moved around the LV, recording ICegrams at different sites and timing them to a stable fixed reference. The aim is to identify the critical diastolic pathway at which the circuit is most susceptible to destruction.

Entrainment of VT

This can only be performed on tachycardias with a re-entry mechanism. The ablation catheter is moved around the ventricle to sites where the circuit is expected (i.e. adjacent to areas of scar). By pacing with this catheter at a rate just faster than the tachycardia cycle length, a VT is entrained if it is following the same circuit but at a faster rate. If the ECG during pacing is a 12/12-lead match to the clinical VT, then this is concealed entrainment. This implies the pacing catheter is within the critical diastolic portion of the circuit. To confirm this when pacing is stopped, the return cycle length (the time from the final paced beat to the next activation at the catheter) should be almost identical to the tachycardia cycle length.

Ablation technique

The standard steps of a VT ablation are:

- induce VT (Wellen's); ensure it is similar to clinical VT and well tolerated
- map VT to identify the critical diastolic pathway:
 - very early local ICegram occurring mid-diastole (50–150 ms ahead of ECG)
 - concealed entrainment during pacing
 - return cycle length (=post pacing interval) < tachycardia cycle length + 30 ms.
- deliver RF energy via an irrigated catheter (for deeper lesion) at the site meeting the criteria above
- if VT is terminated, attempt to reinduce.

Substrate ablation of VT

If VT is not haemodynamically tolerated or cannot be induced, then activation and entrainment mapping cannot be performed. An alternative is to use a 3D mapping system to create a map of the LV during sinus rhythm. The map displays the voltages of the ICegrams, and hence areas of scar are identified. The re-entry circuit of the clinical VT can be estimated from the 12-lead ECG and by pacing at sites on the edge of scar, which, if they are the location of the re-entry circuit driving VT, will give a similar

12-lead ECG appearance to the clinical VT. Ablation is delivered between two areas of fixed conduction block (scar, mitral annulus) to interrupt theoretical re-entry circuits.

Failed ablation

If conventional ablation fails, alternative approaches are:

- ablate the epicardial surface of the heart by delivering the catheter via the pericardium (as for a pericardial aspiration)
- alcohol ablation via a small terminal coronary branch subtending the scarred area supporting re-entry. Hence, give the patient a controlled, small MI that destroys the critical portion of the re-entry circuit
- cardiac surgical ablation.

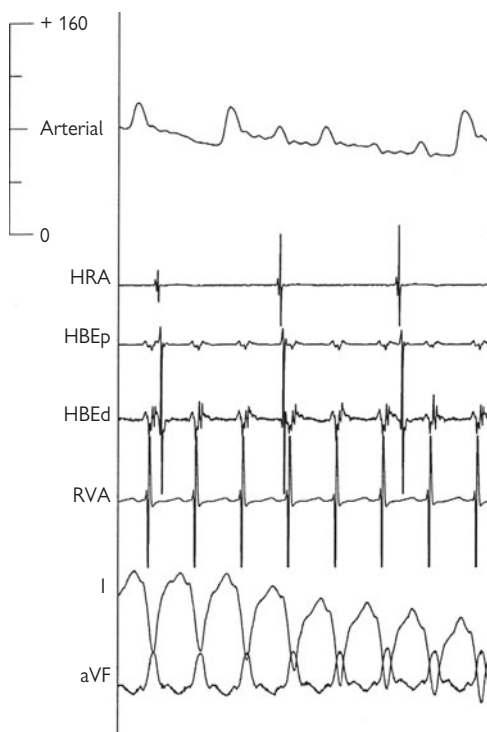


Fig. 11.14 An induced VT at a cycle length of 320 ms (187/min). From top to bottom, a tracing of arterial pressure, high right atrial ICGram, proximal then distal His bundle ICGram, RV ICGram, then two surface ECG leads. There is no V to A conduction at this rate and the atrium is dissociated from the ventricle. Despite the rapid rate, the systolic BP is maintained at 100 mmHg, enabling the VT to be mapped if necessary.


Automatic implantable cardioverter defibrillators

Mirowski implanted the first automatic implantable cardioverter defibrillator (AICD) in 1980 to manage SCD. Since then there has been dramatic improvement in technology, and randomized controlled trial evidence to support their use in primary and secondary prevention. Initial devices were large and placed surgically in abdominal pockets attached to epicardial leads. AICDs are now implanted in the same way as pacemakers and are often part of a biventricular pacing system.

Components

The bulk of an AICD box is the battery and capacitors that generate and store the energy to deliver a defibrillation shock. The box is attached to a ventricular 'shock' lead and often an atrial 'pace-sense' lead. The V lead contains one or two shocking coils and a bipolar set of pacing electrodes at its tip. This both senses electrograms and can deliver low-voltage pulses to pace the heart if it is too slow (bradycardia pacing), or overdrive if it is too fast, e.g. a ventricular tachycardia (antitachycardia pacing, ATP). Microprocessors contain the algorithms that interpret the sensed electrograms to: (1) detect tachycardias; (2) discriminate VT/VF from non-life-threatening arrhythmia (e.g. AF); (3) deliver therapy. These algorithms contain features that are both programmable and non-programmable.

Implantation

AICDs are implanted in the identical way to pacemakers and the same complications occur (see  p. 530). A range of leads are available: active/passive, single coil/dual coil. Extra vigilance is needed over selecting a V lead position with good electrogram sensing (ideally R wave >10 mV). A defibrillation test should be performed once the device is implanted, as ventricular electrograms in VF will be of much lower amplitude than during SR. The patient is sedated and, with the AICD switched on, VF is induced. The device is then observed to ensure it successfully detects and terminates VF. If the device fails, an external biphasic 360 J shock is delivered and the lead is repositioned. During testing, the AICD is programmed to its *least* sensitive detection and delivers an energy that is *at least 10 J* below its maximum output. After the procedure, the AICD is programmed to its *most* sensitive detection and delivers shocks at *maximum* energy. In this way, there is a safety margin that reduces the chance of the device failing.

Indications for AICD

Class I

- Survivors of cardiac arrest secondary to VT or VF when all reversible factors have been excluded (secondary prevention)
- Sustained VT and significant structural heart disease (secondary prevention)
- Syncope of undetermined origin, structural heart disease, and sustained haemodynamically unstable VT or VF induced at EP study
- Previous MI (>40days) + LVEF \leq 35% with New York Heart Association (NYHA) class II–III or LVEF<30% with NYHA class I or LVEF<40% and positive VT stimulation study. Note: all are for primary prevention
- Non-ischaemic cardiomyopathy (LVEF \leq 35%) and NYHA class II–III.

Class IIa

- Sustained VT and reasonable LV function
- Hypertrophic cardiomyopathy (HCM) or ARVC and one or more risk factors for SCD
- VT or syncope in the presence of long QT syndrome, Brugada syndrome, or catecholaminergic polymorphic VT.

Class III (AICD definitely not indicated)

- Patients who are not expected to survive >1 year
- Significant psychiatric co-morbidity that may be worsened by implant or cause problems with follow-up
- VT/VF with a completely reversible cause (e.g. severe systemic sepsis with normal heart), or normal heart VT that is amenable to curative ablation.

Adapted from ACC/AHA/HRS 2008 guidelines. *J Am Coll Cardiol* 51: 2085–105.

AICD programming

Detection of tachycardias

The AICD simply measures the intervals (cycle length) between successive sensed ventricular electrograms, and hence measures ventricular rate. If the rate enters a programmed zone (e.g. >190 bpm), then tachycardia is detected. Most devices allow up to three detection zones, e.g. VT (170–200), fast VT (200–230), and VF (>230). Each zone can be programmed with different therapies. If no therapies are programmed, it is a monitor zone.

Discrimination of SVT from VT/VF

Not all tachycardias at a rate >170 bpm are VT. SVTs such as sinus tachycardia, AVNRT, AVRT, atrial tachycardia, and AF can all reach a V rate >170 bpm. Discrimination algorithms attempt to distinguish these non-life-threatening arrhythmias from VT/VF and prevent delivery of inappropriate and painful therapy. Very fast V rates, e.g. >220 bpm are almost always VT/VF, and discrimination is not applied.

Discrimination of SVT from VT/VF

Discrimination algorithms in AICDs use a combination of the following parameters:

- AV association
 - V>A: always VT/VF
 - V=A: SVT or VT
 - V<A: likely AF or ATach; VT possible (eg AF and VT)
- Electrogram morphology in tachycardia
 - Same as SR: SVT
 - Different from SR: VT or SVT + bundle branch block (BBB)
- Onset of tachycardia
 - Sudden: SVT or VT
 - Gradual: sinus tachycardia
- Stability of VV intervals during tachycardia
 - Not stable: AF or VF
 - Stable: SVT or VT.

Therapies

Once the device detects tachycardia and decides it is definitely VT or VF, it will deliver one of two forms of treatment depending on how the zone has been programmed. Therapies are disabled in a magnetic field.

Antitachycardia pacing (ATP)

This is a burst of pacing that attempts to overdrive and terminate VT, but is not effective for VF. The device delivers a set number of pulses (6–12) at a fixed cycle length that is a percentage of the measured tachycardia cycle length (usually 81%). The sequences may be repeated with shorter cycle lengths (i.e. pace faster). Within the burst of pacing, the cycle length can be shortened (=ramp pacing). If ATP fails to terminate VT, a shock is usually delivered.

Defibrillation

AICDs deliver a maximum energy up to 41 J as a biphasic waveform from the shocking coil on the RV lead to the pulse generator, which is an 'active can'. The shocking vector travels superiorly from the RV, including most of the IV septum and LV. If a dual-coil lead or separate SVC coil is implanted, the device can shock either between both coils or between the can and either coil. All programmed shocks should be at the device's maximum output.

AICD troubleshooting

Follow-up

The patient's AICD is interrogated every 6–12 months either in the clinic or remotely via wireless receivers installed in the patient's home. Checks are made on the lead parameters and battery life (to determine whether a box change is necessary). The arrhythmia log is reviewed to determine if there have been any ventricular or atrial arrhythmias and any therapy delivery. Remote follow-up allows automatic downloads of important events (red alerts), e.g. episodes of VF, impending battery failure, damage to the lead, etc. These are communicated directly to the AICD clinic by urgent email or phone call.

VT/VF storm

This is defined by ≥ 3 appropriate shocks for VT/VF in < 24 hours. Common causes are ischaemia, worsening heart failure, electrolyte imbalance, change in medication, or intercurrent illness. Sometimes no obvious cause can be found. Patients should be managed in specialist EP centres for optimization of antiarrhythmic drugs, device programming, and VT ablation if necessary.

Inappropriate shocks

These are the most important morbidity associated with AICD and occur in 10–20% of patients. A shock delivered in a conscious unsuspecting patient is extremely painful and frightening. Inappropriate shocks can lead to major psychiatric problems of anxiety and depression. They are due to poor programming (human error), VT without haemodynamic compromise, AF with fast ventricular rates, other SVT, lead damage, or external interference (e.g. diathermy). In an emergency, a magnetic placed over the device will disable therapies so the cause can be determined.

Drug interactions

Antiarrhythmic drugs may increase defibrillation thresholds (e.g. flecainide, propafenone, amiodarone). They may also slow the rate of VT such that it no longer falls in the programmed detection zone. Care should be taken to ensure AICDs are still effective after major drug alterations.

End-of-life issues

Patients with advanced heart disease may eventually reach a palliative phase (NYHA class IV) or develop another terminal illness (e.g. cancer). After careful counselling with the patient, family, and palliative care team, it may be appropriate to turn therapies off or not to replace a box that has reached the end of its battery life. These are difficult decisions, and a multidisciplinary approach is necessary. It is important to be aware that devices will need to be turned off when patients have died, and explanted before cremation.

Congenital heart disease

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Specific management issues 606

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Specific conditions (1) 610

Specific conditions (2) 612

Extra-cardiac complications 614

Introduction

Congenital heart disease (CHD) is one of the commonest congenital defects, occurring in approximately 0.6–0.8% of newborns. i.e. there are about 5000 newborns with CHD each year in the UK. Advances in therapy have led to a dramatic improvement in outcome, such that over 85% of infants, even with complex CHD, are expected to reach adolescence and early adulthood. As a result of the success of paediatric cardiology and surgery, *there are now more adults than children with CHD*. In addition, there are patients with structural or valvular CHD who may present late during adulthood. It is estimated that there are approximately 1600 new patients per annum with moderate to complex CHD, of whom 800 might benefit from specialist follow-up in the UK. Most of these patients have had palliative or reparative rather than corrective surgery, and further cardiac operations will be necessary for many.

Role of specialist CHD centres

- Initial assessment of adults with known or suspected CHD
- Surgical and non-surgical interventions, e.g. transcatheter closure of atrial septal defect (ASD)/percutaneous valve implantation
- Continuing care of patients with moderate and complex CHD
- Advice and ongoing support for non-cardiac surgery and pregnancy
- Training new specialists and providing evidence-based clinical decision making
- Providing feedback of late results to refine early treatment

Transition from paediatric to adult care

A smooth transition from the paediatric to the adult CHD specialist is essential. This should be tailored to the individual patient, with inbuilt flexibility. Ideally, a specialist transition clinic should be set up, with input from both the adult and paediatric services. Transfer to the adult unit should occur at around 18 years of age. Patient education about the diagnosis and specific health behaviour, including contraception/pregnancy planning, should be included. Patient passports that include detailed diagrams of the individual cardiac defect and relevant information on topics such as exercise and need for antibiotic prophylaxis should be prepared for each patient.

No patient with CHD should reach adulthood without a clear management plan.

Treat adult CHD with respect. Many problems or errors arise from arrogance or ignorance. The patients may often know more about their condition and its management than the 'emergency' medical team they consult; therefore be patient and listen. Patients are often accompanied by a parent/s even well into late teens/second or third decade. They can prove a great source of information and help; keep them on your side. Increasingly in the UK, adult congenital heart physicians are available for advice, either via email or by telephone. None will refuse a call for help. *Get to know your local specialist centre!*

Disease complexity and hierarchy of care for the adult with congenital heart disease

Level 1

Exclusive care by specialist unit, e.g. Eisenmenger syndrome, Fontan repairs, transposition of the great arteries, any condition with atresia in the name, Marfan

Level 2

Shared care with 'interested' adult cardiologist, e.g. coarctation of the aorta, ASD, tetralogy of Fallot

Level 3

Ongoing management in a general adult cardiology unit, e.g. mild pulmonary valve stenosis, postoperative atrial/ventricular septal defect

Information sources on adult congenital heart disease **1.** Management of grown up congenital heart disease. European Society of Cardiology Task Force Report. *Eur Heart J* 2003;**24**: 1035–1084. **2.** British Cardiac Society Report **3.** Canadian Taskforce Report.

Congenital heart disease in adults

Acyanotic lesions

- Atrial septal defect 📖 p. 610
- Ventricular septal defect 📖 p. 278
- Atrioventricular septal defect 📖 p. 610
- Pulmonary stenosis 📖 p. 610
- Left ventricular outflow tract (LVOT) obstruction 📖 p. 611
- Coarctation of the aorta 📖 p. 611
- Anomalous pulmonary venous drainage 📖 p. 611
- Ebstein's anomaly of the tricuspid valve 📖 p. 613

Cyanotic lesions

- Transposition of the great arteries 📖 p. 612
- Tetralogy of Fallot 📖 p. 612
- Fontan patients 📖 p. 613
- Congenitally corrected transposition of the great arteries 📖 p. 613
- Severe Ebstein's anomaly of the tricuspid valve 📖 p. 613

Assessment of patients with CHD (1)

History

- Family history of CHD
- Exposure to teratogens/toxins during pregnancy
- CHD suspected during pregnancy or at birth (ask the mother!!)
- History of prolonged childhood illnesses
- Prior interventions:
 - any previous hospitalizations for catheter- or surgical-based interventions
 - names of previous paediatric cardiologists and surgeons as well as the unit in which surgery, if any, was performed
- Dental hygiene
- Smoking/drug and alcohol intake

Current symptoms

- Shortness of breath on exertion?
- Ability to climb stairs, hills, walk on the flat, and distance covered?
- Breathless on lying down?
- Chest pain?
 - Precipitating/relieving factors?
 - Any associated symptoms?
- Syncopal episodes?
- Palpitations?
 - Onset, duration
 - Associated pre-syncope/chest pain?
 - Ask patient to tap out rate and rhythm of palpitations
- Assess ability index

General inspection

- Chart the patient's height, weight, and blood pressure (always in the arm opposite thoracotomy scar!) and oxygen saturations
- Does the patient have an obvious syndrome?
 - Down's syndrome (1/3 associated with CHD, especially atrioventricular septal defect)?
 - William's syndrome (supravalvar aortic and pulmonary stenosis)?
 - Noonan's syndrome (dysplastic pulmonary valvular stenosis, hypertrophic cardiomyopathy)?
 - Turner's syndrome (coarctation of the aorta/aortic valve stenosis)?
- Is the patient anaemic or jaundiced?
- Are there any features to suggest infective endocarditis?
- Is there evidence of poor oral hygiene with dental caries or infected gums?
- Any tattoos or body piercing?

Systematic approach to auscultation of a CHD patient

1. Listen to the heart sounds

First heart sound

- The first heart sound is usually heard as a single sound but since mitral closure is loudest, it is best heard at the apex
- A loud first heart sound may be heard in mitral stenosis or sometimes with an ASD
- Soft first heart sounds are a feature of poor myocardial contractility or a long PR interval

Second heart sound

- Fixed splitting in the presence of a significant ASD, and is best appreciated in the high or mid left sternal border
 - Accentuated in the presence of pulmonary hypertension
 - Widely split following repair of tetralogy of Fallot, the second heart sound is reflecting the right bundle branch block (RBBB), characteristic of the post-operative electrocardiogram (ECG)
2. Check for systolic/diastolic murmurs.

(Draw an imaginary line between the nipples)

Murmurs that are loudest above the nipple line

- Ejection systolic in type
- Arise from the right or left ventricular outflow tract (LVOT)
- If associated with a carotid or suprasternal thrill, usually from the left ventricular outflow tract.
- If an ejection click is heard, the murmur is valvar in origin.
- Ejection click of aortic valve stenosis is best heard at the apex.
- Ejection systolic murmur, best heard in the interscapular region and associated with a left thoracotomy, may indicate turbulence across a prior coarctation repair

Murmurs that are loudest below the nipple line

- Pansystolic and arise from mitral/tricuspid regurgitation or from a ventricular septal defect (VSD)
- A 'to and fro' murmur best heard at the upper left sternal edge following cardiac surgery usually results from combined right ventricular outflow tract (RVOT) obstruction and pulmonary regurgitation
- The mid-systolic click and systolic murmur of mitral valve prolapse is best heard with the patient standing up
- A continuous murmur arises from an arterial duct, systemic to pulmonary shunt, or arteriovenous fistulas
- Measure height, weight, blood pressure, and oxygen saturation in all patients. 12-lead ECG is essential at every visit.

Assessment of patients with CHD (2)

Electrocardiogram

- *Rate and rhythm*: consider atrial flutter with variable block if there is a constant rate of 100 or 150/minute—easily confused with ‘sinus rhythm’. Atrial tachycardias are especially common after all forms of atrial surgery e.g. intra-atrial repair for transposition of the great arteries.
- Look for signs of chamber enlargement—atrial or ventricular hypertrophy.
- Assess the presence/absence of bundle branch block.
- Measure the duration of QRS in all post-operative tetralogy of Fallot patients: QRS duration >180 ms is associated with higher risk of arrhythmias, right heart dilatation, and late sudden death.
- If tachycardia is suspected, record 12-lead ECG during administration of IV adenosine.

Role of exercise testing

- Assess heart rate and blood pressure (BP) response to exercise (blunted response in important aortic valve stenosis).
- Compare upper and lower limb BP following coarctation repair.
- Monitor oxygen saturation by pulse oximetry to improve risk stratification in cyanosed patients.
- Also, improves counselling and planning for pregnancy (most frequently used to assess potential impact of pregnancy).
- Formal cardiopulmonary exercise testing is reserved for decision making and retiming of surgical or catheter-based intervention.
- Can help to distinguish limitation due to lack of aerobic fitness, and assess maximal effort.

Chest X-ray

- Chest X-ray (CXR) is a cheap and invaluable investigation in CHD.
- Identify right–left orientation to assess cardiac and visceral positions.
- Assessment of the bronchial branching permits diagnosis of isomeric cardiac defects, e.g. symmetric morphologic right bronchi characteristic of right atrial isomerism (usually associated with complex CHD—common right atria, a common atrioventricular (AV) orifice, a great artery arising from one ventricular chamber and total anomalous pulmonary venous connection).
- Identify situs inversus (mirror image anatomy with liver on the left and stomach bubble on the right with cardiac apex in right chest). Consider Kartagener syndrome. Discordance between the position of the apex and visceral situs is usually associated with CHD.
- Record the cardiothoracic ratio in the notes. Look for rib notching related to collateral blood supply in severe coarctation of the aorta. Assess pulmonary vasculature (see box on next page).

CXR assessment of pulmonary vasculature in CHD patients

Increased vascularity

- Left to right shunt (ASD, VSD)
- Pulmonary oedema
- Obstructed pulmonary venous drainage

Decreased vascularity

- Right ventricular outflow obstruction, e.g. isolated severe pulmonary stenosis, following tetralogy repair
- Pulmonary hypertension

Unilateral increased pulmonary vascular markings

- Consider ipsilateral systemic to pulmonary arterial shunt
- Overperfused major arterial pulmonary collateral artery
- Obstructed pulmonary venous drainage, e.g. following Mustard/Senning intra-atrial repair for transposition of the great arteries

Imaging modalities in CHD

Echocardiography

- This is the most useful investigation in CHD but only when directed by detailed history taking and clinical examination.
- It should be performed by an experienced examiner with detailed knowledge of all aspects of CHD.
- There is no substitute for sequential data, and a protocol for regular, standardized analysis is required.
- Imaging in adults may be limited by poor echogenic windows.

Magnetic resonance imaging (MRI)

- Ideal for the assessment of extra-cardiac pulmonary arterial and venous trees.
- Accurate quantification of valvar regurgitation, e.g. assessment of pulmonary regurgitation and right ventricular function following repair of tetralogy of Fallot.
- Its utility is limited by a scarcity of expert radiologists in the field of CHD. It is rapidly becoming established as providing the most detailed and useful information for decision making in complex CHD.

Cardiac catheterization

- This still has its place in quantifying shunts and obtaining accurate haemodynamic data.
- Increasingly, this is carried out to facilitate percutaneous transcatheter procedures such as occlusion of ASDs.
- With an aging population, many patients with CHD need to undergo coronary angiography, as combined surgical procedures may be required.

Specific signs in patients with CHD

Inspection

Cyanosis or clubbing?

Oxygen saturation should always be measured by pulse oximetry. Central cyanosis is an indication of arterial desaturation and is noted when more than 5 g/dL of reduced haemoglobin is circulating. Thus, it is dependent in part on the total haemoglobin concentration and may be missing in a patient with significant desaturation but who is anaemic. Differential cyanosis implies flow of deoxygenated blood from the pulmonary trunk into the aorta distal to the left subclavian artery, e.g. non-restrictive patent arterial duct with pulmonary vascular disease and right-to-left shunt.

Previous operation scars?

Lift the patient's arms and look for evidence of thoracotomy scars. Is the apex beat displaced or even in the right chest? Assess co-morbidity, e.g. scoliosis and respiratory dysfunction related to prior lateral thoracotomy.

Jugular venous pulse (JVP)

This can give information about conduction effects and arrhythmias, waveform, and pressure. Increased resistance to atrial filling results in an exaggerated 'a' wave, which may occur in isolated severe pulmonary stenosis or in tricuspid atresia. Episodic 'cannon' waves occur in cases of heart block when the atrium contracts against a closed tricuspid valve. A prominent 'v' wave is characteristic of tricuspid regurgitation.

Palpation

- Feel all the pulses, including the femorals. Coarctation of the aorta is a clinical diagnosis.
- Check the blood pressure in the upper and lower limbs, palpating the posterior tibial artery with the cuff inflated around the calf.
- Bounding pulses are characteristic of severe aortic regurgitation, patent arterial duct, or the presence of a surgical systemic to pulmonary arterial shunt (Blalock–Taussig).
- An increase in the right brachial pulse may reflect the Coanda effect of supravalvar stenosis in patients with Williams' syndrome. Thrills may be felt in the femoral vessels, reflecting AV malformation following prior cardiac catheterization.
- Check the position of the apex beat. Also, check that the liver and stomach are in the correct position. Situs inversus with the apex in the right chest is the mirror image of normal; 95% of patients with mirror image dextrocardia have no co-existing congenital cardiac disease. Situs solitus with the apex in the right chest is invariably associated with CHD, and is often complex and unpredictable.
- A parasternal heave represents right ventricular overactivity, most marked when there is both pressure and volume overload of the chamber, such as following repair of tetralogy of Fallot.
- A palpable second sound in the upper left intercostals space is detected when pulmonary hypertension is present.

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Surgical operations for CHD (1)

Congenital heart surgery in adolescents and adults should only be undertaken in specialist centres. There are three categories:

- patients who have not undergone prior operations
- patients who have undergone previous palliative operations
- patients who have undergone previous reparative procedures.

Re-do sternotomy, preservation of myocardial performance, and attention to pulmonary bed vascular abnormalities and aorto-pulmonary collaterals require careful prior planning and close co-operation between the surgeon, cardiac anaesthetist, cardiologist, and intensive care team.

Blalock–Taussig shunt

This is a procedure for systemic to pulmonary arterial shunt, using a subclavian arterial flap (classical) or Gore-Tex[®] tube (modified) to increase pulmonary blood flow and improve oxygenation in cyanotic congenital heart disease. This is a palliative procedure which has superseded earlier operations such as Waterston shunt (ascending aorta to right pulmonary artery) or Pott's shunt (descending aorta to left pulmonary artery).

Coarctation of the aorta

This is relieved by either a subclavian flap approach or direct end-to-end anastomosis. Occasionally, a bypass graft is required in adult patients, from the ascending to descending aorta.

Glenn shunt

The superior vena cava (SVC) is anastomosed to the ipsilateral pulmonary artery as a means of improving oxygenation in infants or young children. This is usually confined to patients with 'single' ventricles and univentricular circulations. In its classical form, the right pulmonary artery was detached from the main pulmonary artery. The bidirectional Glenn shunt was fashioned such that blood from the SVC entered both pulmonary arteries.

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Surgical operations for CHD (2)

Tetralogy of Fallot (see Fig. 12.1)

This is treated by closure of the ventricular septal defect with a patch of pericardium or Gore-Tex[®] and relief of the RVOT obstruction by trans-annular patching, valvectomy, or placing a homograft/conduit between the right ventricle and pulmonary artery.

Rastelli operation (see Fig. 12.2)

This is usually undertaken in patients with complex CHD, e.g. transposition of the great arteries with large VSD. The VSD is closed by a large patch in such a way as to connect the left ventricle to the aorta, and a conduit or homograft connects the right ventricle to the pulmonary artery (PA).

Ross operation

This is an alternative to aortic valve replacement, which may be attractive to younger patients, especially females. The diseased aortic valve is removed with the coronary arteries detached. The patient's own pulmonary valve is resected and placed in the aortic position with the coronaries reattached. A homograft is placed between the right ventricle and the pulmonary artery.

Fontan operation

This represents the definitive palliation for patients with effectively uni-ventricular circulations such as mitral or tricuspid atresia. Blood from the superior and inferior vena cava is directed to the pulmonary arteries without the benefit of a subpulmonary ventricle. Oxygenated blood returns to the systemic ventricle and is then pumped to the aorta.

Mustard/Senning operations (see Fig. 12.3)

These are life-saving innovations for treatment of patients with transposition of the great arteries, which involve intra-atrial redirection of oxygenated and de-oxygenated blood to the systemic and pulmonary systems respectively. The right ventricle serves as the systemic subaortic ventricle. The procedures have been largely abandoned because of late problems with arrhythmias, pathway obstruction, and ventricular failure.

Arterial switch

This has largely superseded the Mustard/Senning procedure. The aorta and pulmonary artery are relocated to their original positions, with re-anastomosis of the coronary arteries to the neo-aorta.

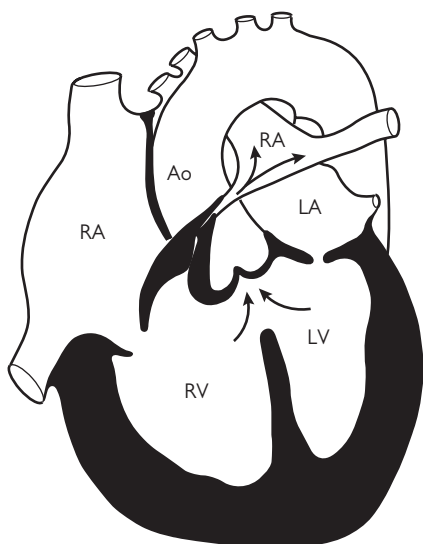


Fig. 12.1 Tetralogy of Fallot. Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

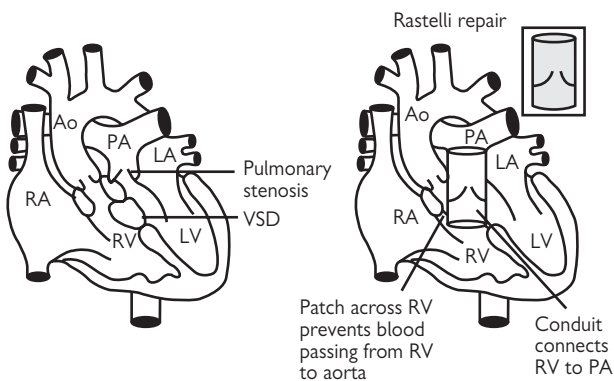


Fig. 12.2 The Rastelli operation. PA = pulmonary artery.

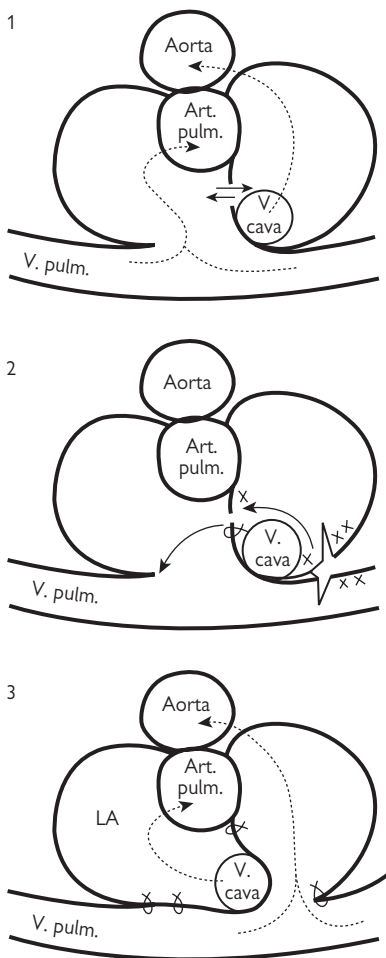


Fig. 12.3 The Senning operation. Redrawn from Koustantinov, IE et al. (2004). Atrial switch operation: past, present, and future. *Annals of Thoracic Surgery*, **77**: 2250–8, with permission.

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Percutaneous transcatheter interventions for CHD

Balloon atrial septostomy

This is a life-saving intervention in neonates with transposition of the great arteries in which an atrial communication is created by tearing a hole in the atrial septum using a balloon catheter. It can be performed at the bedside under echocardiographic control.

Pulmonary valvuloplasty

This is the procedure of choice for patients of all ages with pulmonary valvar stenosis. It is less successful if the valve is dysplastic (Noonan's syndrome). The pulmonary valve annulus is measured by echocardiography or angiography, and a balloon (100–120% diameter) is used. It is one of the most effective transcatheter interventions.

Aortic valvuloplasty

This is of limited use in adults. If the aortic valve is pliable but not calcified, balloon dilatation may defer the need for definitive surgery but usually at the expense of aortic regurgitation. The balloon size should not exceed the size of the aorta at the site of the valve attachment. An antegrade approach via a trans-septal puncture is advised, to reduce the incidence of valve damage.

Atrial septal defect

Most secundum atrial septal defects are amenable to percutaneous closure. The Amplatzer[®] septal occluding device is made of nitinol (a nickel titanium alloy with inherent shape memory) and comprises two discs with a self-centring waist. The defect may be balloon sized under transoesophageal echocardiographic (TOE) guidance. Defects up to 40 mm in size can be closed providing there are sufficient rims (>5 mm) to the pulmonary veins and the attachment of the mitral valve. As a rule of thumb, patients with pulmonary arterial pressures <70 mmHg can proceed to ASD closure. This is not suitable for any atrial defects other than those of the secundum variety, i.e. sinus venosus defects or partial atrioventricular septal defects. Procedural complications are rare in expert hands. Antiplatelet agents are administered for three to six months until the device has completely endothelialized. Transient headaches are common in the weeks following closure but serious complications are rare. These include transient ischaemic episodes/stroke, atrial arrhythmias, and embolization of the device. Remember that concomitant electrophysiological procedures may need to be undertaken in patients with significant atrial arrhythmias.

Ventricular septal defects

Indications for closing defects in adults are limited, and the procedure is most frequently employed in patients with ischaemic VSD. Occasionally, 'small' defects can produce volume overload of the left ventricle over time and require closure. Such defects may be amenable to transcatheter occlusion using the Amplatzer[®] peri-membranous or muscular occluding devices.

This should only be undertaken in specialist centres. Complete heart block and device embolization have been described.

Coarctation of the aorta

Surgical correction in the adult is a major challenge, with its associated risk of paraplegia. All patients have an aortopathy which renders the aortic tissue very friable. Both native and re-coarctation of the aorta can now be successfully treated by transcatheter balloon dilatation and stenting. Covered stents may be required for native coarctation, to reduce the incidence of dissection and rupture. MRI is invaluable in patient selection and for selecting stent size. This intervention should only be undertaken in specialist centres where expert surgical help is readily available. Remember that balloon dilatation of previous patch aortoplasty carries the highest risk of aortic rupture. Lifelong surveillance is necessary to detect aneurysm formation.

Patent arterial duct

This may occasionally present in later life. If small or medium-sized with no pulmonary hypertension, most can be successfully occluded with a variety of transcatheter occluding devices or coils.

Pulmonary valve implantation

Percutaneous transcatheter implantation of a bovine jugular venous valve mounted within a platinum–iridium stent into the right ventricular outflow tract is now possible. This procedure, if it stands the test of time, will revolutionize our approach to management of patients with pulmonary regurgitation following right heart congenital surgery, offering as it does a non-surgical approach. These valves have been used in patients with right ventricle to pulmonary artery homografts which are leaking or stenosed, as well as in native outflow tracts. Increasingly, transcatheter aortic valve implantation is employed in patients with significant risk factors for surgery.

Specific management issues

Complications of cyanotic CHD

Chronic hypoxaemia results in an increased red cell mass and total blood volume. This compensatory mechanism may initially enhance oxygen delivery; however, symptoms of hyperviscosity may develop.

- *Symptoms of hyperviscosity*: headaches, visual disturbances (blurred or double vision), impaired alertness, fatigue, paraesthesia, tinnitus, myalgia, muscle weakness, restless legs, transient ischaemic events or stroke.
- Measure haemoglobin and red cell indices; most patients have a compensated erythropoiesis with a stable haemoglobin.
- Therapeutic phlebotomy should be reserved for symptomatic patients e.g. haemoglobin >20 g/dL or haematocrit >65%. Symptoms may be relieved by removal of 500 mL (maximum) of blood with concomitant fluid replacement with dextrose or saline. Phlebotomy should be performed no more than twice per annum as it increases the risk of stroke by causing iron deficiency. Intravenous line filters should always be used.

Iron deficiency in a polycythaemic patient should be aggressively treated with oral iron supplementation (ferrous sulphate 600 mg/day), recheck haemoglobin 8–10 days later.

- Oral iron is poorly tolerated by many patients (abdominal pain, diarrhoea, constipation) and compliance is often poor. Furthermore, particularly in patients with systolic heart failure, oral iron is poorly absorbed and prolonged courses are needed to correct the deficiency. This may also be the case in patients with cyanotic heart disease and high venous pressure (liver congestion and high portal pressure). Therefore we prefer to use intravenous iron therapy in many patients.

How is iron sucrose given?

- Iron sucrose: 5 mL vial containing 100 mg
- The standard dose is 200mg (2 vials, 10 mL)
- A small test dose, e.g. 2 mL should be given on the first occasion, followed by the remaining 8 mL after waiting 10 minutes
- It is quite safe to give it undiluted as a slow push over 10 minutes
- Subsequent administrations do not require a test dose

Iron therapy, including the first dose, can be given safely in the outpatient clinic and this is the preferred setting. If patients live outside London and are unable to attend the clinic three times a week, they should be admitted to the ward.

Skin

- Severe acne is common in cyanotic congenital heart disease.
- It can act as a source of infection and endocarditis.
- Treat aggressively.

Gallstones

- Common in cyanosed patients.
- Bilirubin is a product of haemoglobin breakdown.
- Suspect if the patient presents with severe abdominal pain/discomfort.

Renal function

- Reduced glomerular filtration rate.
- Increased levels of creatinine.
- Abnormalities in clearance of uric acid frequently accompany chronic cyanosis, and gout, sometimes frank, may result.
- Cautious use of contrast in angiography is advised, and always pre-hydrate.

Non-cardiac surgery

- This should be undertaken in specialist centres with care delivered by a multidisciplinary team.
- Use local anaesthesia if possible; otherwise use a cardiac anaesthetist with experience in CHD.
- Consider preoperative phlebotomy if haemoglobin >20 g/dL or haematocrit >65%.
- Air line filters should be employed.

Antibiotic prophylaxis

New guidelines have been released by the National Institute for Health and Clinical Excellence (NICE). Antibiotic prophylaxis is no longer recommended for dental procedures. However, there are differences between these recommendations and those from the European Society of cardiology (ESC) and America. Many cardiologists still recommend antibiotic prophylaxis for patients with a previous history of endocarditis or with a mechanical valve. Patient attention to maintaining good dental hygiene is essential.

Arrhythmia

- Arrhythmia is an important cause of morbidity and mortality and major cause for hospitalization of CHD patients. It may lead to significant haemodynamic deterioration and is poorly tolerated.
- It may be due to:
 - underlying cardiac defect, e.g. atrial isomerism
 - part of natural history, e.g. haemodynamic changes such as chamber enlargement or scarring
 - residual postoperative abnormalities.

Management

Specialist advice is essential. New presentation demands a complete haemodynamic assessment including electrophysiological investigation. Correction of any underlying postoperative haemodynamic abnormality may be one of the most important therapeutic interventions.

- Record a 12-lead ECG.
- Administer IV adenosine whilst recording the ECG. The mode of termination of the tachyarrhythmia may give very useful information on its aetiology, e.g. pre-excitation.
- Urgent DC cardioversion may be required if haemodynamic compromise is present. Ideally, TOE should rule out intracardiac thrombus. If the patient is on warfarin, always check the international normalized ratio (INR) as well as the serum electrolytes prior to cardioversion.

Pregnancy

The majority of women with CHD can tolerate pregnancy.

But

- Congenital heart disease is now the major cause of maternal cardiac death in developed countries, All need specialist counselling *before* embarking on pregnancy.
- Cardiologists are woefully ill-prepared to give such advice—paediatric cardiologists sometimes more so!
- All young women of child-bearing age should undergo a detailed clinical and haemodynamic assessment, which should include a formal exercise test and detailed cross-sectional echocardiography with emphasis on systemic ventricular function. They should be reviewed by a cardiologist with a special interest in maternal cardiology.
- All women with complex CHD should be closely monitored in specialist centres, where delivery should take place. Multidisciplinary input is essential.
- Pregnancy is contraindicated in some CHD patients.

Women with CHD in whom pregnancy is contraindicated

- Pulmonary hypertension
 - e.g. Eisenmenger syndrome (50% maternal and fetal mortality; maternal death may occur up to two weeks post-partum)
- Heart failure, e.g. secondary to failing Fontan circulation
- Women with severe cyanosis and polycythaemia:
 - if saturation is less than 80% at rest and haemoglobin is greater than 18 g/dL, there is a greater incidence of miscarriage and intrauterine growth retardation
 - severe outflow tract obstruction, e.g. severe aortic stenosis

Contraception

- Should be tailored to the patient and her cardiac condition
- For patients at risk of venous thromboembolism, newer progesterone-only pills (Cerazette®) or implants (Nexplanon®) are advised.
- Emergency contraception such as Levonelle® can be used when no contraception has been used, or when the usual method has failed. It can be taken by all patients.

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Specific conditions (1)

Atrial septal defect

This is one of the commonest lesions, presenting for the first time in adult life. It is often missed as clinical signs of fixed splitting of the second heart sound can be difficult to appreciate. It may present for the first time with new-onset atrial flutter or fibrillation. Consider the need for electrophysiological interventions, e.g. Maze procedure for atrial fibrillation. Shunting tends to increase with aging as the left ventricle stiffens. Closure is indicated in all symptomatic patients . . . few are truly asymptomatic when assessed by cardiopulmonary testing! There is no upper age limit. The vast majority of secundum defects are amenable to transcatheter closure. Pulmonary hypertension needs to be excluded but most patients with PA pressures <70 mmHg can safely undergo closure. Atrial arrhythmias are one of the common late medical problems. All other types such as sinus venosus defect (defect in the upper atrial septum associated with overriding of the SVC and anomalous right pulmonary venous drainage) and partial AV septal defect require surgical closure. A sinus venosus defect represents a major surgical challenge involving redirection of the anomalous pulmonary vein(s). The risk of endocarditis is very low. Antibiotic prophylaxis is not indicated.

Ventricular septal defect

The majority are small as they are usually repaired in childhood. Eisenmenger syndrome (pulmonary vascular disease associated with reverse, right-to-left shunting via intracardiac communication—VSD, ASD, patent ductus arteriosus (PDA)) is becoming increasingly rare. VSD should be closed if there is significant shunt, previous endocarditis, development of aortic regurgitation, or RVOT obstruction. It is always important to demonstrate reversibility of pulmonary hypertension prior to intervention. It may be amenable to surgical or transcatheter closure. Ventricular arrhythmias may occur late during follow-up.

Atrioventricular septal defect

This is a common defect in patients with Down's syndrome. If unoperated, pulmonary vascular disease (Eisenmenger syndrome) develops. Left AV valve regurgitation/stenosis are the major determinants of need for further interventions. Valve replacement may be necessary.

Pulmonary stenosis

This may present for first time in adult life. It can be successfully treated by balloon valvuloplasty, which should be undertaken if the valve gradient exceeds 30 mmHg on Doppler echocardiography. Surgery is reserved for calcified and dysplastic valves. The outlook is excellent. The risk of endocarditis is low.

Left ventricular outflow tract obstruction

Aortic valve stenosis is especially common in association with a bicuspid valve. This is a complex lesion and an aortopathy is commonly present. There is a risk of aortic dilatation and dissection. The degree of stenosis or regurgitation may increase over time. Effort intolerance, chest pain, or syncope, especially with exertion, need to be taken seriously and intervention considered. It may occasionally be amenable to balloon valvuloplasty but more commonly requires surgical intervention. Aortic valve replacement (lifelong anticoagulation) or homograft insertion/Ross operation (no anticoagulation but potential need for further interventions, critically operator dependent) can be offered. Subaortic stenosis is uncommon (no ejection click) and requires surgical resection if severe or the patient is symptomatic. Recurrence is possible. Supravalvar stenosis is commonly seen in patients with Williams' syndrome. It may be associated with multiple stenoses in the origins of the coronary arteries and the aortic arch arterial branches. Reconstructive surgery is complex.

Coarctation of the aorta

Most patients seen in adult clinics will have already undergone surgery. Some may present for the first time with hypertension. Always feel the femoral pulses! Consider Turner's syndrome in female patients. Coarctation of the aorta is a complex lesion usually associated with a bicuspid aortic valve (ejection click at the apex) and aortopathy. During follow-up, upper (right arm) and lower limb BP should be recorded and evidence of left ventricular hypertrophy (LVH) on ECG and cross-sectional echocardiography should be noted. Re-coarctation may occur over time and should be suspected if there are reduced femoral pulses or radiofemoral delay on examination. Doppler echocardiography can help by revealing an increased systolic velocity signal with forward flow through the site of re-coarctation during diastole. MRI with three-dimensional reconstruction is the imaging modality of choice. Transcatheter balloon dilatation and stenting is feasible in many patients, thus avoiding the risks of thoracic aortic surgery. Lifelong surveillance is necessary to rule out aneurysm formation or recurrence.

Anomalous pulmonary venous drainage

Many patients will undergo surgery in early childhood. This may occur in association with Scimitar syndrome. If the patient is symptomatic (shortness of breath, arrhythmia) and there is evidence of right heart volume overload, for example on the cross-sectional echocardiogram, consider surgery. There is a low risk of endocarditis.

Specific conditions (2)

Transposition of the great arteries

The aorta arises from the right ventricle, and the pulmonary artery from the left ventricle. This is the commonest cyanotic cardiac lesion presenting in the first few days of life. In the absence of mixing at cardiac or great arterial level, this condition is uniformly lethal. The majority of adult survivors have undergone intra-atrial repair by Mustard or Senning procedure. These produced excellent early survival but significant late morbidity and mortality. Common late problems are atrial arrhythmias (flutter/fibrillation), venous baffle narrowing, and right ventricular failure with tricuspid regurgitation. Arrhythmias are poorly tolerated and prompt restoration to sinus rhythm is essential. Baffle stenosis can be relieved by transcatheter balloon dilatation/stenting. Ventricular failure requires intensive medical therapy but ultimately may necessitate cardiac transplantation. Patients who have undergone the arterial switch procedure are now reaching early adulthood. Problems with coronary arterial stenoses at the site of re-anastomosis to the neo-aorta have been identified in some.

Tetralogy of Fallot

This comprises a large non-restrictive VSD, over-riding aorta, right RVOT obstruction, and right ventricular hypertrophy. This is the commonest cyanotic cardiac lesion presenting outside the neonatal period. If it presents with critical cyanosis in the neonatal period, the patient may undergo a palliative Blalock–Taussig shunt prior to complete repair in early childhood. Many centres now opt for definitive repair even in the first few months of life. The vast majority of adults will have undergone some form of repair with surgical closure of the septal defect and relief of the RVOT obstruction. Arrhythmias are an inevitable consequence of surgery (scarring, ventriculotomy, and pulmonary regurgitation). Late arrhythmias (both atrial and ventricular) and sudden death occur. Pulmonary regurgitation, ignored for many years as a benign condition, is now known to be one of the most important causes of morbidity and mortality in patients following RVOT surgery. The QRS duration >180 ms on the ECG has been used as a marker for patients at risk of arrhythmia and late sudden death. Patients should be assessed by exercise testing and MRI. A percutaneous approach to pulmonary valve implantation is available, using a bovine jugular venous valve mounted within a platinum–iridium stent, and is suitable for patients with severe pulmonary regurgitation and outflow tracts <20 mm in size. Branch pulmonary arterial stenoses should be treated aggressively by catheter intervention. Surgical insertion of a homograft valve is currently performed, with perioperative mortality less than 1% in specialist centres. The majority of such conduits need replacing within a 10-year period, i.e. there is a need for multiple re-operations. Aortic regurgitation may also occur.

Fontan patients

This is the definitive palliation for patients born with 'single ventricle' physiology, in which all the systemic venous return is directed back to the lungs without the benefit of a subpulmonary ventricle, e.g. mitral/ tricuspid/pulmonary/aortic atresia. It produces excellent early and mid-term survival but late failure occurs even in the most carefully selected candidates. The late problems comprise atrial arrhythmias including sinus node dysfunction and heart block, AV valve regurgitation, ventricular failure, venous obstruction, and protein-losing enteropathy (<50% 5-year survival). The failing Fontan is a major challenge, and transplantation or conversion to a more streamlined modification with concomitant arrhythmia surgery should be considered.

Cardiac transplantation is rarely undertaken in adults with CHD. This relates to lack of organs, prior antibodies, complex anatomy, previous sternotomies, and collaterals with risk of bleeding. There is a lack of suitably qualified surgical teams. Heart–lung transplantation is rarely if ever undertaken for patients with either complex cyanotic CHD or Eisenmenger syndrome.

Congenitally corrected transposition of the great arteries

Cyanosis is present if there is associated VSD and pulmonary stenosis or if there is pulmonary vascular disease with VSD and no pulmonary stenosis. This is a rare lesion with prolonged survival in some, if there is an isolated lesion. There is an ongoing risk of complete heart block (2% per annum). AV valve regurgitation in association with systemic right ventricular failure is a major long-term problem.

Ebstein's anomaly of the tricuspid valve

This condition is associated with apical displacement of the tricuspid valve and is associated with atrial communication. Cyanosis occurs via right-to-left shunt at atrial level. There is a wide spectrum of presentation, depending on the severity of tricuspid valve regurgitation and associated anomalies. In infancy, this presents with heart failure and cyanosis, and prognosis is poor. In the older child or young adult, the murmur may be an incidental finding, and mild forms can be asymptomatic. Atrial arrhythmias are common and associated with pre-excitation (accessory pathways). Intervention is warranted if symptomatic with heart failure, severe tricuspid regurgitation, or arrhythmias. Newer surgical techniques involving reconstruction of the tricuspid valve have been introduced, with superior outcomes. Tricuspid valve replacement/repair can be offered as a last resort. Interatrial communications causing cyanosis/paradoxical emboli can be closed percutaneously if haemodynamic assessment permits.

Extra-cardiac complications

Polycythaemia: Chronic hypoxia stimulates erythropoietin production and erythrocytosis. The 'ideal' haemoglobin level is ~17–18 g/dL; some centres advocate venesection to control the haematocrit and prevent hyperviscosity syndrome. Follow local guidelines. Generally consider phlebotomy only if moderate or severe symptoms of hyperviscosity are present and haematocrit >65%. Remove 500 mL of blood over 30–45 minutes and replace volume simultaneously with 500–1000 mL saline, or salt-free dextran (if heart failure). Avoid abrupt changes in circulating volume. If hyperviscosity symptoms are the result of acute dehydration or iron deficiency, venesection is not required and the patient must be rehydrated and/or treated with iron.

Renal disease and gout: Hypoxia affects glomerular and tubular function, resulting in proteinuria, reduced urate excretion, increased urate reabsorption, and reduced creatinine clearance. Overt renal failure is uncommon. Try to avoid dehydration, diuretics, and radiographic contrast. Asymptomatic hyperuricaemia does not need treatment. Colchicine and steroids are first-line agents for treatment of acute gout. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided.

Sepsis: Patients are more prone to infection. Skin acne is common, with poor healing of scars. Skin stitches for operative procedures should be left in for 7–10 days longer than normal. Dental hygiene is very important due to the risk of endocarditis. Any site of sepsis may result in cerebral abscesses from metastatic infection or septic emboli.

Thrombosis and bleeding are multifactorial and are caused by a combination of abnormal platelet function, coagulation abnormalities, and polycythaemia. Prothrombin time (PT) and activated partial thromboplastin times (aPTT) values may be elevated and secondary to a fall in factors V, VII, VIII, and X. Both arterial ± venous thromboses and haemorrhagic complications (e.g. petechiae, epistaxes, haemoptyses) can occur. Dehydration or oral contraceptives are risk factors for thrombotic events. Spontaneous bleeding is generally self-limiting. In the context of severe bleeding, general measures are effective, including platelet transfusion, fresh frozen plasma (FFP), cryoprecipitate, and vitamin K. Aspirin and other NSAIDs should generally be avoided to decrease the chances of spontaneous bruising/bleeding.

Primary pulmonary problems include infection, infarction, and haemorrhage from ruptured arterioles or capillaries.

Stroke: Can be both thrombotic and haemorrhagic. Arterial thrombosis, embolic events (paradoxical emboli in R→L shunt) and injudicious phlebotomy lead to spontaneous thrombosis. Haemostasis problems, especially when combined with NSAIDs or formal anticoagulation, can lead to haemorrhagic stroke. Any injured brain tissue is also a nidus for intracranial infection/abscess formation.

Complications secondary to drugs, investigations, surgery: Avoid abrupt changes in BP or systemic resistance. Contrast agents may provoke

systemic vasodilatation and cause acute decompensation. They may also precipitate renal failure. Before non-cardiac surgery, try to optimize haematocrit and haemostasis by controlled phlebotomy and replacement with dextran. High-flow oxygen is important before and after surgery. Extreme precaution is required with IV lines.

Arthralgia: Is mainly due to hypertrophic osteoarthropathy. In patients with R→L shunt, megakaryocytes bypass the pulmonary circulation and become trapped in systemic vascular beds, promoting new bone formation.

Haemoptysis is common. Most episodes are self-limiting and precipitated by infection. Differentiation from pulmonary embolism may be difficult. Try to keep the patient calm and ensure adequate BP control. Give high-flow oxygen by mask. If there is clinical suspicion of infection (fever, sputum production, leukocytosis, raised C-reactive protein (CRP), etc.) start broad-spectrum antibiotics. Ventilation–perfusion (VQ) scan may help in the diagnosis of pulmonary embolism but is often equivocal. Avoid aspirin and NSAIDs as these exacerbate the intrinsic platelet abnormalities. There is anecdotal evidence for the use of low-dose IV heparin, dextran 40 (500 mL IV infusion q4–6h), Arvin[®] (reduces plasma fibrinogen by cleaving fibrin), or low-dose warfarin therapy for reducing thrombotic tendency in these patients. Severe pulmonary haemorrhage may respond to aprotinin or tranexamic acid.

Breathlessness may be due to pulmonary oedema or hypoxia (increased shunt) secondary to chest infection or pulmonary infarction. Do not give large doses of diuretics or nitrates as this will drop systemic pressures and may precipitate acute collapse. Compare CXR to previous films to try to assess if there is radiological evidence of pulmonary oedema. The JVP in patients with cyanotic CHD is typically high and should not be used as a sole marker of heart failure. Overall, patients need a higher filling pressure to maintain pulmonary blood flow. Give high-flow oxygen by mask. Start antibiotics if there is a clinical suspicion of infection. Give oral diuretics if there is evidence of pulmonary oedema or severe right heart failure. Monitor haematocrit and renal function closely for signs of over-diuresis.

Effort syncope should prompt a search for arrhythmias, in particular ventricular tachycardia (VT) (Holter monitor), severe valve disease, or signs of overt heart failure. Treat as appropriate.

Chest pain may be secondary to pulmonary embolism or infarction (spontaneous thrombosis), pneumonia, ischaemic heart disease, or musculoskeletal causes. It requires careful evaluation with the conventional diagnostic modalities already described.

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Coronary artery disease in patients with rheumatologic diseases

Origins

- Atherosclerosis, thrombosis, arteritis, vasospasm

Epidemiology

Systemic lupus erythematosus (SLE)

- The prevalence of ischaemic heart disease (IHD) is 6–10% (true prevalence of subclinical disease not known). Women with SLE are overall 5–6 times more likely to have a myocardial infarction (MI) than non-lupus women of similar age.

Rheumatoid arthritis (RA)

- Incidence 4.8–5.9/1000 person-years. Patients with RA are 2–3 times more likely than matched controls to have a MI, after controlling for traditional risk factors.
- Epicardial disease is more common than microvascular disease.
- Patients with acute coronary syndrome (ACS) have a twofold recurrence rates risk and mortality compared with age- and sex-matched controls.
- Coronary arteritis is uncommon; it affects epicardial and small/medium-sized intramyocardial arteries and usually presents as ACS.

Inflammation and atherogenesis

- There is evidence that inflammation has a fundamental role in the initiation and progression of atherosclerosis.
- Increased risk of IHD cannot be fully explained by traditional atherogenic risk factors (hypertension, hyperlipidaemia, diabetes mellitus, smoking, obesity, sedentary lifestyle).
- Disease or treatment-related risk factors: elevated homocysteine, glucocorticoid use, renal disease (SLE), seropositive disease (RA), and non-steroidal anti-inflammatory drug (NSAID) use (probably by increasing blood pressure).

Differential diagnosis of chest pains

- IHD: maintain lower than normal threshold for investigating and appreciate it as a cause in younger patients
- Primary coronary artery thrombosis (antiphospholipid syndrome)
- Upper gastrointestinal problems associated with NSAID use
- Costochondritis
- Osteoporotic rib/vertebral fracture
- Pleuropericarditis
- Large-vessel vasculitis causing aortic dissection or aneurysm

Management

- Physician awareness and patient education
- Manage traditional risk factors: aggressive blood pressure control, lipid-lowering agents, smoking cessation

- Individualized aerobic exercise programme
- Disease-specific potential risk factors: reduce homocysteine levels (consider folate supplementation), minimize glucocorticoid use, recognize thrombotic potential; consider antiphospholipid antibodies

See Table 13.1.

Table 13.1 Cardiac manifestations of rheumatic diseases

	Pericardial disease	Myocardial disease	Valvular disease	Aortic root disease	Coronary disease	Conduction system disease
Ankylosing spondylitis	+	+	++	++		+
Behçet's disease	+		+	+	+	
Churg–Strauss syndrome		+			+	
Giant cell arteritis		+	+	++	+	
Kawasaki's disease					+++	
Neonatal lupus erythematosus		+				++
Polyarteritis nodosa					+	
Polymyositis/dermatomyositis	+	+				+
Reiter's syndrome			+			
Rheumatoid arthritis	+++	+	+	+	++	
Adult Still's disease	++	+		+		+
Systemic lupus erythematosus	+++	+	++		++	+
Systemic sclerosis	++	++				++
Takayasu's arteritis		+	++	+++	+	+
Wegener's granulomatosis					+	

Taken from Manzi S, Kao AH, Wasko MM *Oxford Textbook of Rheumatology*, Chapter 13.4 The cardiovascular system. Oxford: Oxford University Press.

Rheumatoid arthritis

- RA is a multisystem inflammatory autoimmune disease characterized by a symmetrical and progressive deforming, peripheral arthropathy.
- Prevalence 1%; male:female = 1:3, peak onset in the fifth decade.

Clinical features

- Constitutional symptoms such as fever, malaise and fatigue
- Symmetrical polyarthritis with insidious or abrupt onset
- Early morning and rest stiffness
- Subcutaneous nodules
- Pleuritis, interstitial lung disease, intrapulmonary nodules
- Scleritis, episcleritis, dry eyes

Cardiac disease

Coronary artery disease

- See  p. 618.

Pericarditis

- 50% of cases have a benign fibrinous pericarditis with effusions seen in 40% of cases on echocardiography
- 1–2% of cases are symptomatic
- Usually independent of disease duration and may precede it
- Cardiac tamponade and constrictive pericarditis are rare
- Responds to treatment with steroids and disease-modifying drugs

Myocardial and endocardial granulomas

- Found in more than 50% of patients with subcutaneous nodules
- Rarely, they compromise cardiac function through mitral valve deformity and regurgitation
- Rarely, they cause conduction problems like first-degree (commonest), left bundle branch, and complete heart blocks

Myocarditis

- 20% of patients with severe disease have a diffuse myocarditis with non-specific inflammatory infiltrates, myocyte necrosis, and fibrosis
- May rarely cause biventricular failure, arrhythmias, and conduction problems
- Ventricular function may also be compromised by secondary amyloidosis

Valvular disease

- Non-specific valvitis producing fibrotic, hyalinized valves with occasional incompetence. The aortic valve is affected more commonly than the mitral valve

Treatment

- Immunosuppressive therapies such as disease-modifying anti-rheumatic drugs (DMARDs) (e.g. methotrexate), Anti-TNF (tumour necrosis factor) therapies and rituximab
- Early intensive treatment (often with combinations of therapies) to tightly control disease activity prevents joint damage and progression to disability

RA predictors of coronary artery disease

- Older age of disease onset
- Early corticosteroid therapy
- Longstanding disease (>10 years)
- Active extra-articular disease
- Active erosive and nodular disease
- Vasculitis
- High serum titres of rheumatoid factor
- High levels of haptoglobin
- Erythrocyte sedimentation rate (ESR) >55 mm/h.

Systemic lupus erythematosus

- Multisystemic autoimmune disease affecting predominately women; female:male = 9:1, peak onset in 20s and 30s,
- Prevalence per 100 000 estimated at 35 in Caucasian and 177 in African-Caribbean individuals in the UK¹
- Associated with accelerated atherosclerosis (see 📖 p. 212)
- Pulmonary hypertension may occur though more frequent in scleroderma and mixed connective tissue disease (see 📖 p. 627)

Pericarditis

- Symptomatic pericarditis occurs in approximately 25% of SLE sufferers at some point in their disease. Autopsy studies show pericardial disease in 61–100%. The pericardial fluid is usually exudative.
- Pericarditis is commonly associated with pleurisy and/or pleural effusion.
- It is frequently associated with active disease in other organs, so full assessment of disease activity is required, including urinalysis, urine protein/creatinine ratio, anti-dsDNA, and complement levels.
- Unusually for SLE, the C-reactive protein (CRP) is usually high, and there may also be a fever.
- Rub is rarely audible; diagnosis is confirmed by electrocardiography (ECG) or ECHO.
- Complications such as pericardial tamponade and constrictive pericarditis are rare, and invasive therapy is not usually required.
- There is usually a prompt response to prednisolone therapy; this may suggest the need for escalation of other disease-modifying therapy.

Myocarditis

- Myocarditis is a vasculopathy rather than true myositis; creatine kinase (CK) is usually normal.
- Diagnosis is usually clinical, based on global ventricular hypokinesia in the context of active disease. Myocardial biopsy, despite the risk of sampling error, remains the gold standard for diagnosis.
- Prevalence by echocardiography is 1–20%.
- Clinically apparent disease usually requires high-dose corticosteroid therapy and escalation of therapy to include other immunosuppressive therapy (such as pulsed cyclophosphamide) in addition to standard heart failure therapy.

Valvular heart disease

- Valve abnormalities are found in 28–74%, most commonly of the mitral valve followed by the aortic valve. Other valves and endocardial surfaces may also be affected. It may cause valve regurgitation; stenosis is rare.
- Libman–Sack's (verrucous) endocarditis occurs in 4–43% of cases; it is more frequently found in those with antiphospholipid antibodies.

Valve leaflet thickening occurs in 19–52% of cases, with associated regurgitation in 73%.

- There is no evidence for the use of immunosuppression or anticoagulation therapy despite the association with complications.

Conduction defects

- Conduction defects can be detected in up to 5% of patients but complete heart block is restricted to case reports.

Antiphospholipid syndrome

- This is an acquired autoimmune thrombophilia that causes both arterial and venous thrombosis and pregnancy morbidity.
- Diagnosis requires the detection of anti-cardiolipin, anti- β_2 -protein antibodies, or lupus anticoagulant, confirmed after 12 weeks to ensure persistence.
- It may be primary or secondary to other connective tissue diseases, particularly SLE.

Valvular disease

- Valve abnormalities are found in 30–32% of cases, particularly those with peripheral arterial thromboses. Vegetations occur in 6–10% and thickening in 10–24%.
- As with SLE, the mitral valve is most frequently affected, followed by the aortic valve. There is no evidence for immunosuppression or anticoagulation.

Thrombotic disease

- Although rare, MI may occur due to primary thrombotic disease despite normal angiography. Pulmonary veno-occlusive disease may cause pulmonary hypertension. A micro-angiopathic cardiomyopathy has also been described.

Neonatal lupus

- Neonatal lupus is associated with the transplacental transmission of anti-Ro antibodies and anti-La antibodies.
- It is not limited to women with lupus, and frequently the mothers have other connective tissue diseases or are asymptomatic.
- The predominant manifestations are photosensitive neonatal lupus rash and congenital heart block, but other organs may be involved.
- With the exception of heart block and myocardial disease, the disease resolves with the clearance of maternal antibodies.

Congenital heart block

- Congenital heart block occurs in approximately 2% of the offspring of anti-Ro antibody-positive mothers, with a recurrence rate in subsequent pregnancies of around 17%.
- There is frequently associated myocardial disease.
- It usually presents between 18 and 30 weeks of gestation.
- Early mortality occurs in approximately 20%.
- Complete heart block is irreversible, 1st- and 2nd-degree heart block may respond to therapy. Betamethasone or dexamethasone should be considered.
- First-degree heart block detected *in utero* frequently resolves spontaneously. Pre-emptive therapy is not recommended, fluorinated steroids and beta-stimulation may be beneficial in fetuses that are compromised.


Systemic sclerosis

- Systemic sclerosis is characterized by scleroderma proximal to the metacarpal phalangeal joints, Raynaud's, oesophageal dysmotility, calcinosis, and telangiectasia.
- *Limited systemic sclerosis*: scleroderma is confined to the face and distal limbs in 70% of cases; associated with anti-centromere antibodies. *Diffuse systemic sclerosis*: patients are more likely to develop lung, cardiac, and renal disease and have a poorer prognosis in 30% of cases. Associated with anti-Scl70 antibodies.
- Following therapeutic advances (particularly for renal hypertensive crisis), cardiac disease and pulmonary hypertension have become more prominent causes of death, with pulmonary hypertension second only to pulmonary fibrosis.

Cardiac disease

- Myocardial fibrosis is found in 50–80% of cases in autopsy studies and in 2/3 of cases using delayed enhanced magnetic resonance imaging (MRI).
- No immunomodulatory therapy has been shown to alter the progression of myocardial fibrosis.
- It is associated with atrial and ventricular arrhythmias, cardiac failure and sudden death.

Pulmonary hypertension and connective tissue diseases

- Pulmonary arterial hypertension is the most frequent cause of death in systemic sclerosis (occurs more frequently in limited systemic sclerosis).
- It also occurs in the other connective tissue diseases, predominantly mixed connective tissue disease and SLE.
- In addition to pulmonary vascular disease, patients are also at risk of pulmonary hypertension secondary to interstitial lung disease or veno-occlusive disease related to the antiphospholipid syndrome.
- Patients at high risk, namely ribonucleoprotein (RNP)-positive mixed connective tissue disease and systemic sclerosis should be screened annually for pulmonary hypertension by echocardiography and lung function testing (including transfer factor).
- Due to the high pregnancy mortality in women with pulmonary hypertension, RNP-positive patients and those with systemic sclerosis should also be screened before conception.
- In contrast to systemic sclerosis, there are some retrospective data to suggest that a proportion of patients with SLE and mixed connective tissue disease may respond to cyclophosphamide therapy. Thus, in addition to the therapies discussed on  p. 622, immunosuppressive treatment should be considered in these patients.

Polymyositis and dermatomyositis

- Cardiac disease is the main cause of death in polymyositis (PM) and dermatomyositis (DM) after malignancy and interstitial lung disease. However, it is unclear whether this is due to accelerated atherosclerosis or myocarditis.
- 25% of cases have myocarditis at post-mortem, with microscopic interstitial fibrosis, non-specific inflammatory infiltrates, and necrosis. Ventricular function is usually preserved. However, disease that is severe enough to cause cardiac failure is rare.
- Conducting tissues may be affected, producing non-specific ST- and T-wave changes, atrial arrhythmias, and atrioventricular and bundle branch block. These are more commonly seen in children.
- Clinically apparent pericarditis is rare but is seen in 25% on echocardiography.
- Cor pulmonale may occur secondary to primary lung disease or pulmonary hypertension.
- Overt myocarditis should be treated using steroids and immunosuppressive drugs.

Mixed connective tissue disease

- This group of patients has high-titre anti-RNP antibodies and clinical features of scleroderma, SLE, and inflammatory myositis. As such, they may have the cardiac manifestations of any of these connective tissue diseases. Pericarditis is the commonest cardiac manifestation, found in 10–30% patients. Pulmonary hypertension has a prevalence of approximately 13% and is a major cause of death. Patients should have annual screening for pulmonary hypertension.

Sjögren's syndrome

- This predominantly affects the exocrine glands, causing dry eyes and dry mouth secondary to lacrimal and salivary gland disease.
- Anti-Ro and anti-La antibodies are a hallmark of the disease, and as such there is a small risk of congenital heart block in the offspring of affected women. However, heart block in Sjögren's patients is rare.
- Clinically apparent cardiac disease is rare as a manifestation of Sjögren's syndrome. However, subclinical diastolic function and asymptomatic pericarditis may be common.

Takayasu arteritis

- This is an idiopathic, segmental, granulomatous, large-vessel vasculitis predominantly involving the aorta and its branches.
- UK incidence: 0.15/million; 80–90% female in their 2nd/3rd decade.
- Symptoms are non-specific and symptoms include fever, fatigue, weight loss, myalgia, arthralgia, and rash, frequent at onset.
- Limb claudication, abdominal pain, and syncope are due to arterial disease producing end-organ ischaemia.

Investigations

- Arterial biopsy is not usually feasible; thus imaging is core to diagnosis.
- Imaging demonstrates the characteristic stenoses, occlusions, and/or aneurysms of the aorta and its primary branches.
- Arteriography is usually diagnostic but invasive—cannot assess arterial wall thickness. Magnetic resonance angiography (MRA) and/or computed tomography (CT) angiography is usually used. Ultrasound is also helpful. Positron emission tomography (PET) may show increased uptake in active disease.
- Bloods are non-specific; there are usually raised inflammatory markers.
- Echocardiogram is used to assess the ventricles, aortic root, and valve.

Cardiac complications

- Heart failure from central hypertension due to stenotic lesions
- Aortic regurgitation secondary to aortitis
- Angina and MI from ostial or coronary arteritis.

Treatment

- High-dose steroids; additional agents used include methotrexate, azathioprine, leflunomide, and anti-TNF therapy, but evidence is limited.
- Balloon angioplasty/stenting or surgery may be complicated by restenosis due to ongoing inflammation.

Giant cell (temporal) arteritis

- This is characterized by granulomatous large- and medium-vessel vasculitis occurring in individuals aged ≥ 50 years. Incidence is 1/500 in this age group
- Features: visual disturbance/loss, jaw claudication, and temporal headaches. Polymyalgic symptoms may be present
- High inflammatory markers
- Temporal artery biopsy is diagnostic but may be normal due to patchy involvement

Cardiac complications

- Aortitis and aortic valve disease may occur.
- Thoracic aneurysms are a late complication occurring in approximately 10% of cases and may progress to dissection.
- Coronary artery involvement is also recognized.

Treatment

- High-dose steroids. Two randomized controlled trials (RCTs) assessing methotrexate had conflicting results. Retrospective data suggest low-dose aspirin may reduce the risk of cranial ischaemic events and visual loss.

Kawasaki disease

- There is arteritis of large, medium, and small arteries, particularly the coronary arteries.
- UK incidence: ~8/100 000 children; 90% at <10 years (peak 18–24 months in USA and 6–12 months in Japan). Male>female. It is more common in children of Far-East descent.

Clinical features

Acute stage (days 1–11): High fever, irritability, non-exudative bilateral conjunctivitis (90%), iritis (70%), perianal erythema (70%), acral erythema and oedema that impede ambulation, strawberry tongue, lip fissures, hepatic, renal, and gastrointestinal dysfunction, myocarditis, pericarditis, mitral and, rarely, aortic regurgitation, and cervical lymphadenopathy (75%).

Subacute stage (days 11–30): Persistent irritability, anorexia, conjunctival infection, decreased temperature, thrombocytosis, acral desquamation, and aneurysm formation.

Convalescent/chronic phase (after 30 days): Aneurysm expansion, possible MI, and resolution of smaller aneurysms (60% of cases).

Investigations

- Blood abnormalities are non-specific: raised inflammatory markers (ESR, CRP), normocytic anaemia, granulocytosis, thrombocytosis (weeks 2–3), and thrombocytopenia (with severe coronary disease), mild transaminitis (40%) and raised bilirubin (10%).
- Echocardiogram to detect coronary aneurysms (4% with intravenous immunoglobulin (IVIG) therapy, 20–25% untreated or aspirin alone), impaired cardiac function, valvular heart disease, and pericardial effusions. Perform at diagnosis, 2 weeks, and 6–8 weeks after diagnosis in uncomplicated cases.
- In patients with aneurysms, serial monitoring with echocardiography.
- In chronic disease, stress testing, angiography, spiral CT, and/or cardiac MRI may be required to assess or monitor disease.

Treatment

- Aspirin 30–100 mg/kg daily for 4 days, and thereafter, 3–5 mg/kg daily. If no coronary aneurysms, treatment can be stopped after resolution of inflammation. As there is a risk of Reye's syndrome, annual influenza vaccine should be given if there is long-term use.
- Intravenous gammaglobulin (2 mg/kg) within 10 days of onset of symptoms. Further courses may be tried in resistant cases. Consider in patients presenting later if there are aneurysms or ongoing inflammation.
- In refractory disease, other agents such as methylprednisolone or infliximab (an anti-TNF agent) may also be considered.

- In chronic disease, in patients with giant aneurysms, due to the risk of coronary thrombosis, anticoagulation or additional platelet therapy should be considered.
- In a small minority of patients, coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), or valvular heart surgery is required.

Differential diagnosis of Kawasaki disease: diseases and disorders with similar clinical findings

- Viral infections (e.g. measles, adenovirus, enterovirus, Epstein–Barr virus)
- Scarlet fever
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome
- Bacterial cervical lymphadenitis
- Drug hypersensitivity reactions
- Stevens–Johnson syndrome
- Juvenile rheumatoid arthritis
- Rocky Mountain spotted fever
- Leptospirosis
- Mercury hypersensitivity reaction (acrodynia).

Small- and medium-vessel vasculitis

- Polyarteritis nodosa and Churg–Strauss vasculitis affect medium and small vessels.
- Both may be complicated by coronary artery involvement or myocarditis, which are poor prognostic factors for survival.
- The presence of cardiac disease is an indication for cyclophosphamide therapy.

Churg–Strauss syndrome

- This is systemic vasculitis characterized by allergic rhinitis, late-onset asthma, blood eosinophilia, and eosinophilic pulmonary infiltrates. Cutaneous and peripheral nerve involvement is common.
- Peak onset is at 38 years, but it can occur throughout adulthood, and is usually preceded by a prodromal allergic phase.
- Anti-neutrophil cytoplasmic antibodies (ANCA) are present in 38–59% patients, usually of the myeloperoxidase subtype.

Polyarteritis nodosa

- ANCA-negative vasculitis.
- Characterized by mesenteric arteritis (abdominal pain, weight loss), livedo reticularis, renal involvement (hypertension), and peripheral nerve involvement.
- Hepatitis B surface antigen positive in 30% of cases; hepatitis C and hairy cell leukaemia are also implicated in a subset of cases; these patients require different therapeutic regimens.
- Selective angiography remains the gold standard for diagnosis.

Small vessel vasculitis

ANCA-positive vasculitis

- Wegener's granulomatosis, and microscopic polyangiitis are small-vessel ANCA-positive vasculitides.
- Pauci-immune glomerulonephritis is common in both.
- Wegener's granulomatosis rarely causes pericarditis and coronary arteritis (10–20% cases ante-mortem); they can cause MI and sudden death.
- Microscopic polyangiitis may be complicated by coronary artery involvement or myocarditis, which have a major effect on the prognosis.

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Ankylosing spondylitis

- Incidence 0.1–1%; 1–2% amongst human leucocyte antigen (HLA)-B27-positive individuals. 10–20% of first-degree relatives positive for HLA-B27 develop the disease. Male:female = 3:1.
- Usually seen in northern Europeans. Onset is in late adolescence/early adulthood.
- Other seronegative spondyloarthropathies include reactive arthritis (Reiter's syndrome), and those in association with psoriasis and inflammatory bowel disease.

Cardiac involvement

- Usually manifests late; occasionally precedes overt joint disease
- Aortic regurgitation (1–10%) causes: (1) ascending aortitis (1–10% cases); (2) aortic valve fibrosis causing cusp thickening, nodularity, and shortening
- Anterior mitral valve leaflet thickening, rarely causing mitral regurgitation
- Fibrosis of the aortic and mitral valve junction producing subaortic bump on echocardiography
- Pericarditis (<1% of cases)
- Myocardial fibrosis causing systolic and diastolic dysfunction on echocardiography. May progress to dilated cardiomyopathy. Myocardial function may be further compromised by secondary amyloidosis
- Atrioventricular node conduction problems with complete heart block

Clinical features

- Systemic features: malaise, fever and weight loss
- Insidious low back pain progressing proximally in a relapsing–remitting pattern
- Chronic pain and morning stiffness (>70% cases); fatigue (65% cases); reduced mobility (47% cases). Depression (20% cases, especially females) and neurological deficits
- Acute unilateral iritis (25–30% cases)
- Chest tightness and breathlessness from restricted chest movements

Imaging

- Imaging of sacro-iliac joints (plain X-ray, MRI, bone scan): erosions and sclerosis of sacroiliac joints (sacro-iliitis)
- Squared-off vertebral bodies and syndesmophytes culminating in the bamboo spine

Bloods

- No diagnostic tests; there may be elevated ESR and CRP (75% of cases)

Treatment

- NSAIDs, steroids, immunosuppressants, including anti-TNF
- Specialist treatment for complications. May require spinal or cardiac surgery

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Marfan syndrome

Epidemiology

- This is one of the commonest single gene mutation diseases. Incidence is 1/ 5000 to 1/10 000.
- There are no known geographical, racial, or sex predilections.
- It is diagnosed prenatally through to adulthood.

Pathology

- Autosomal dominant point mutations in fibrillin-1 gene on chromosome 15. Over 200 are described. Phenotype is highly variable due to varying genotype expression.
- Fibrillin-1 glycoprotein is an integral component of microfibrils in connective tissues. The structural integrity of ocular, skeletal, cardiovascular, and other tissues is compromised.

Ghent criteria for diagnosis

- Index case—no contributory family or genetic history, major criteria in at least two different organ systems plus involvement of a third organ system. Alternatively, contributory family or genetic history, one major organ system criterion plus involvement of a second organ system.
- Relative of index case—major criterion in family history, major criterion in organ system plus involvement of a second organ system.

Imaging

- Radiographs, CT, and MRI to assess the axial skeleton, hips, hands, and feet.
- Echocardiography and MRI scan to assess the mitral and aortic valves, aortic root, and ascending aorta. If the measured aortic root dimension is greater than that expected from a normogram by 1.18 times, there is root dilatation.
- Slit-lamp examination looking for retinal detachment, superolateral lens dislocation, cataracts, severe myopia, and open-angle glaucoma. Globe ultrasound and keratometry to assess the cornea.

Genetic testing

- Genetic testing has a limited role in diagnosis; it is used primarily to diagnose family members if a mutation is known. Linkage analysis is used in families with several affected relatives.

Treatment

- β -blockers (possibly calcium-channel blockers) delay and attenuate aortic root dilation
- Antibiotic chemoprophylaxis for bacteraemia-prone procedures
- Surgery for aortic root and valve disease, skeletal and ocular complications
- Gentle exercise

Prognosis

- Life expectancy is about two-thirds of normal.
- Cardiovascular death in over 90% of cases is due to aortic dissection or heart failure.

Ghent criteria for Marfan syndrome

Skeletal system involvement

(two major or one major and two minor criteria)

Major criteria	Minor criteria
1. Pectus carinatum	1. Moderately severe pectus excavatum
2. Pectus excavatum requiring surgery	2. Joint hypermobility
3. Reduced upper to lower segment ratio or arm span to height ratio >1.05	3. High arched palate with teeth crowding
4. Wrist and thumb signs	4. Facial appearance (dolichocephaly, malar hypoplasia, down-slanting palpebral fissures, retrognathia) or
5. Scoliosis exceeding 20° or spondylolisthesis	5. Enophthalmos
6. Elbow extension <170°	
7. Medial displacement of the medial malleolus causing pes planus, or	
8. Protrusio acetabulae	

Ocular system involvement (one major or two minor criteria)

Major criteria	Minor criteria
1. Ectopia lentis	1. Abnormally flat cornea
	2. Axial globe lengthening
	3. Iris or ciliary muscle hypoplasia

Cardiovascular system involvement

(one major or one minor criterion only)

Major criteria	Minor criteria
1. Ascending aortic dilation involving at least the sinuses of Valsalva with or without aortic regurgitation and	1. Mitral valve prolapse with or without mitral regurgitation
2. Ascending aortic dissection	2. Main pulmonary artery dilatation
	3. Mitral annulus calcification
	4. Descending thoracic or abdominal aortic dilatation or dissection

Pulmonary system involvement (requires one minor criterion)

1. Spontaneous pneumothorax or apical blebs

Skin and integument involvement (requires one of the following):

1. Striae atrophicae without marked weight change, pregnancy, or repetitive stress, or
2. Recurrent or incisional herniae

(Continued)

Dural involvement (one major criterion)

1. lumbosacral dural ectasia

A contributory *family or genetic history* (one major criterion)

1. Parent, child, or sibling meeting diagnostic criteria independently
2. Known fibrillin-1 mutation *or*
3. Presence of haplotype around fibrillin-1 inherited by a descendent known to be associated with unequivocally diagnosed Marfan syndrome in the family

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Ehlers–Danlos syndrome

Epidemiology

- 1 in 5000 live births; incidence is about 1 in 400 000
- Typically presents between childhood and early adulthood
- No racial or sex bias is known.

Pathology

- Inherited (autosomal dominant or recessive and X-linked recessive) defects in synthesis and metabolism of different types of collagen producing connective tissue defects
- A new form has recently been described due to a deficiency of tenascin-X (extracellular matrix protein) with normal collagen
- Six subtypes: classic, hypermobile, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis. There is much overlap between types in up to 50% cases.

Clinical features

- Joint hypermobility, skin hyperextensibility, tissue fragility, and poor wound healing. Patients classically get 'cigarette paper' scarring over the knees.
- Mitral valve prolapse is seen in classic, hypermobile, and vascular forms. A minority of patients progress to severe mitral regurgitation requiring surgery. Recent echocardiographic studies suggest cardiac defects are less frequent than previously thought, although coronary artery aneurysm can be devastating.
- Aortic root ectasia with dilated sinuses of Valsalva is also seen. Rarely, severe or progressive and aortic root replacement is exceptional.
- The vascular form also exhibits prominent veins, low weight, short stature, spontaneous pneumothorax, and rupture of medium- and large-sized arteries and bowel perforation. Joints are affected less frequently. The skin is fragile but not hyperextensible.
- Differential diagnoses include Marfan syndrome, Menkes kinky hair disease, Williams syndrome, Stickler syndrome, cutis laxa, and pseudoxanthoma elasticum.

Treatment

- There is no specific medical therapy. High-dose vitamin C may provide some benefit there are but no controlled studies
- Patient education and preventive strategies. Avoid excess and repetitive lifting, and contact sports
- Avoid suturing wounds if possible
- Regular eye and dental assessments
- Antibiotic chemoprophylaxis for mitral valve prolapse
- Genetic counseling; there is a limited role for genetic testing

Prognosis

- Increased mortality in vascular form. Median age is 50 years, with death from spontaneous arterial and gastrointestinal rupture.
- Other forms usually have normal life expectancy, with increased morbidity from recurrent dislocations, poor wound healing, and scarring.

Rheumatic drug therapy and the heart

Only rheumatic drug therapies with specific relevance to the cardiovascular system are considered here.

NSAIDs and cyclo-oxygenase (COX)-2 inhibitors

- A 2006 meta-analysis of clinical trials found that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high-dose regimens of ibuprofen and diclofenac, but high-dose naproxen is not associated with such an excess.¹
- Associated with a tenfold risk of symptomatic heart failure in patients with a history of cardiac disease (and doubling of risk in those without).²

Glucocorticoids

- Avoided for long-term control of disease activity in view of adverse side-effect profile.
- High-dose steroid is associated with adverse effects on the cardiovascular system: endothelial dysfunction, impaired glucose tolerance and hypertension.
- Association of steroids with atherosclerosis is not clear. Some studies have shown a protective effect of low-dose steroid. It may be that by reducing inflammation they have protective effects.

Anti-TNF therapies

(e.g. adalimumab, etanercept, infliximab)

- Immunosuppressive/immune-modulatory effect.
- Anti-TNF therapy is contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure.
- Patients who develop new-onset heart failure while on anti-TNF therapy should have therapy discontinued and be evaluated for other causes of heart failure, keeping in mind that underlying diseases themselves may be causative.

Zoledronic acid

- In a double blind placebo-controlled RCT of 3889 participants, serious atrial fibrillation occurred more frequently (50 vs. 20) in the zoledronic acid group compared with controls.³

1 Kearney, PM, Baigent C, Godwin J, et al. (2006). Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ (Clin Res ed)* **332**(7553): 1302–8.

2 Page J, Henry D (2000). Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med* **160**(6): 777–84.

3 Black D, Delmas P, Eastell R, et al. (2007). Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* **356**: 1809–22.

Peri-operative management of anti-TNF

- British Society of Rheumatology guidelines recommend withholding treatment with anti-TNF for patients with RA 2–4 weeks prior to major surgery.
- Treatments may be restarted postoperatively if there is no evidence of infection and once wound healing is satisfactory.
- Interrupting immune-suppression may trigger flares of disease.
- Flares of rheumatoid arthritis can often be managed with oral/intramuscular steroid (e.g. Depo-Medrone[®]).

Erectile dysfunction

Definition

Erectile dysfunction (ED) is the inability to achieve or maintain a penile erection that is sufficient for satisfactory penetrative sexual intercourse.

Epidemiology

- Currently 150 million men worldwide have ED
- ED increases with age
- 40% of men over 40 years have ED
- 70% of men over 70 years have ED

Causes

- In men over 30 years of age, vascular causes are the most common—endothelial dysfunction (atherosclerosis)
- The incidence of ED in diabetes is over 70%, and in hypertension it is over 60%
- Psychological (usually younger men with premature ejaculation), neurological (multiple sclerosis, Parkinson's disease, radical non-nerve-sparing prostatectomy), endocrine (diabetes, hypogonadism), drug related (antihypertensives, antidepressants)
- Obesity, physical inactivity, depression, hyperlipidaemia, smoking, alcohol excess
- Coronary disease (50–75% of men)
- Metabolic syndrome

Investigations

- Fasting glucose, lipid profile
- Hypothyroid check
- Testosterone (free) and sex-hormone-binding globulin (SHBG) before 11 am
- ED is a marker for asymptomatic cardiovascular disease (CVD) occurring 2–5 years before a cardiac event—assess CVD risk (e.g. blood pressure (BP))
- Waist measurement

Treatment (general)

- Sensitive counselling
- Ask routinely (men take up to 3 years to volunteer their ED)
- Minimize CVD risk
- Lifestyle advice (smoking, weight, exercise)
- If ED occurs within 1 month of starting a drug (e.g. thiazide), change medication
- Assess physical fitness for sexual intercourse

Treatment (specific)

Phosphodiesterase type 5 (PDE-5) inhibitors

- Sildenafil, tadalafil, vardenafil
- On demand or daily therapy (tadalafil)

- Titrate to effect
- Not with nitrates or nicorandil (hypotension risk)
- Require stimulation (not aphrodisiacs)
- Take one hour before intercourse for full effect and last 6–8 hours (sildenafil, vardenafil) or 36 hours (tadalafil)
- 80% success rate (60% in individuals with diabetes)
- Act to prevent breakdown of cyclic GMP (smooth muscle relaxant) by PDE5, prolonging relaxation
- Common side-effects are headache, flushing, indigestion, and nasal congestion
- Uncommon, blue vision (sildenafil), back pain (tadalafil)
- Caution with alpha-blockers

Prostaglandins

- Alprostadil by intracavernosal injection or pellet inserted into the urethra
- Dose titrated to effect (10–15 minutes)
- Powerful smooth muscle relaxant
- Injections once a day, three times a week maximum, over 80% successful (erection lasts 30–60 minutes)
- Pellets daily, success 45% (not popular)
- Careful technique needed
- Priapism 1–2%; fibrosis <1%
- Injections can cause pain and haematoma, and pellets burning
- Avoid with penile curvature or high risk of priapism (leukaemia, sickle cell disease)
- Manual dexterity problems—partner to inject

Vacuum devices

- Failed PDE-5 inhibitors or contraindicated
- Sucks blood in and rubber band holds it in
- Bruising sometimes with anticoagulants
- Lack of spontaneity, penis feels cold

Penile implants

- Specialist referral

Testosterone

- A low testosterone <10 nmol/L increases CVD risk
- Affects sex drive as well as ED
- Low levels <12 nmol/L reduce success of PDE-5 inhibitors
- Measure before 11 am
- Replace with topical gel/patches or injections

Summary

ED is common, destroys relationships, and leads to depression and lack of self-esteem. Treatment requires asking, advising, and tailoring therapy to lifestyle advice and is successful in over 80% of cases. ED is a marker for asymptomatic CVD.

Chronic kidney disease as a cardiovascular risk factor

Chronic kidney disease (CKD) is a powerful cardiovascular (CV) risk factor and, conversely, cardiac dysfunction tends to impair renal function. A consensus group suggested renal evaluation in patients with cardiac problems.

The assessment of renal function is based primarily on two parameters, the *glomerular filtration rate* (GFR) and *urinary excretion of albumin* (in more advanced stages of CKD there is unselective proteinuria). In early stages of CKD, a major reduction of GFR is still compatible with serum creatinine concentrations within the normal range because serum-creatinine depends also on non-renal factors, particularly muscle mass. More accurate estimates of GFR (eGFR) are possible by measurement of serum-creatinine with validated methodology (Cleveland Clinic Protocol) and by correcting for age, sex, and ethnicity:

$$\text{eGFR} = 175 \times (\text{standardized serum creatinine}) - 1.154 \times (\text{age}) - 0.203 \times 0.742 (\text{for females}) \times 1.212 (\text{for black individuals})$$

At an eGFR >60 mL/min/1.7 m², the above estimate becomes imprecise and such numerical values should not be reported. In this range, cystatin C is more precise than eGFR, but the measurement is costly and currently not routinely available.

Apart from GFR, *urinary excretion of albumin* is a powerful predictor of CV risk. For historic reasons, one still distinguishes between normoalbuminuria and microalbuminuria (definition: 30–300 mg albumin/day), but the cardiovascular risk increases steadily even in the range of normoalbuminuria. The most convenient and adequately sensitive procedure is to measure albumin in the morning urine without correction for urinary creatinine concentration.

Both GFR and albuminuria independently contribute to CV risk. In the absence of albuminuria, the CV risk conferred by reduced renal function is markedly less.

Impaired renal function impacts on CV risk not only in patients with primary kidney disease, but reduced renal function is also a major risk factor for cardiac events in patients with primary cardiac disease, particularly coronary heart disease and congestive heart failure. The mechanisms by which renal impairment affects cardiac function include:

- ↑blood pressure
- sympathetic overactivity and reduced breakdown of catecholamines (renalase)
- lipid abnormalities, e.g. Lp(a), small dense low-density lipoprotein (LDL), remnants, modified apolipoproteins
- increased oxidative stress and microinflammation
- increased serum phosphate (a novel powerful CV risk factor) and the phosphaturic hormone FGF23
- asymmetric-dimethyl arginine (ADMA).

A major cause of CV risk is elevated blood pressure. Renal patients, particularly diabetic patients with nephropathy, are characterized by nocturnal non-dipping, and because of vascular stiffening by increased blood pressure amplitude. Ambulatory blood pressure measurements are a valuable tool. To halt progression of CKD and to reduce CV risk, current guidelines recommend a *target blood pressure* of 130/80 mmHg (or even lower values if proteinuria exceeds 1 g/day) in patients with diabetic and non-diabetic CKD.¹ In patients with coronary heart disease, it is wise to not lower systolic BP to values <130 mmHg and diastolic BP <70 mmHg. Renin-angiotensin system (RAS) blockade further intensifies reduction of proteinuria, in part independently of blood pressure. Cardiac arrest (sudden death) is the most frequent cause of death, followed by heart failure and death from other cardiac causes, e.g. aortic valvular disease. MI is more frequent than in the background population but accounts only for roughly 9% of deaths.

In CKD, particularly in uraemia, patients develop cardiac hypertrophy (both left and right ventricle), cardiac fibrosis, microvessel disease with reduced coronary reserve and reduced capillary density, and reduced ischaemia tolerance, and in dialysed patients stunning is frequently observed during dialysis sessions.

¹ Mancia G, De Backer G, Dominiczak A, et al. (2007). 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* **25**: 1751–62.

CKD: which examinations are appropriate?

Initial renal work-up of a *patient with cardiac problems* should include assessment of eGFR and albuminuria or proteinuria, respectively. If there is a suspicion of primary kidney disease, also carry out urinary sediment and renal ultrasonography; if renovascular disease is suspected, use duplex sonography.

Initial cardiological work-up of the *patient with renal disease* includes ECG and echocardiographic evaluation to detect inappropriate left ventricular (LV) hypertrophy, LV malfunction, and, in advanced stages, pericardial effusion. In patients with endstage kidney disease, metabolic myopathy of skeletal muscles usually precludes meaningful evaluation by treadmill testing. Pharmacological stress testing permits non-invasive ischaemia detection (particularly relevant if renal transplantation is under consideration). MRI technology is very helpful but application of gadolinium is contraindicated in advanced CKD (see later).

Coronary angiography remains the gold standard for the diagnosis of coronary artery disease (CAD). It is often underused due to concerns about radiocontrast nephropathy, but should definitely not be withheld in patients with acute coronary syndrome.

To assess large-vessel disease as an important contributor to CV risk, pelvic and abdominal X-ray to assess calcification of the iliac arteries and aorta are sensible.

Side-effects of cardiological investigations in patients with CKD

Acute renal failure is a feared complication of radiocontrast administration in CKD patients, particularly in those with diabetes. Mortality is significantly increased by radiocontrast nephropathy (odds ratio up to 5–10). Long-term outcome is worse in patients with acute renal failure and pre-existing CKD; even after recovery from an episode of acute renal failure, the risk of delayed progression to endstage kidney disease is high.

The best prevention is adequate hydration, reduction or temporary cessation of diuretic treatment, and avoidance of drugs that predispose to kidney damage (NSAIDs, aminoglycosides, etc.). It is controversial whether blockade of the RAS aggravates or reduces the risk of acute renal failure.

The only effective prophylaxis is administration of normal saline. The evidence for sodium bicarbonate or N-acetyl-cysteine is not convincing.


The influence of the type of radiocontrast agent administered is currently uncertain. Isosmolar radiocontrast agents are more viscous, and it has been suggested to reduce renal risk by warming up of the radiocontrast.

MRI, using gadolinium-containing contrast agents is contraindicated in advanced CKD because of the risk of acute reactions and chronic toxicity, i.e. nephrogenic systemic fibrosis.¹

¹ Thomsen HS (2009). How to avoid nephrogenic systemic fibrosis: current guidelines in Europe and the United States. *Radiol Clin North Am* **47**: 871–875, vii.

Prevention and treatment of cardiovascular sequelae in renal patients

Limited controlled evidence is available, but current strategies for prevention and treatment include those listed next:

- The most important component of treatment is *blood pressure control* (see  Chronic kidney disease as a cardiovascular risk factor, p. 646). In patients on hemodialysis, antihypertensive medication increases the risk of hypotensive episodes during fluid removal by ultrafiltration.
- *Reduction of salt intake* facilitates blood pressure lowering and reduces proteinuria (a predictor of progression of renal function loss).
- *Blockade of the RAS*: inappropriate activation of the RAS is a hallmark of CKD. RAS blockade confers benefit beyond blood pressure lowering and mitigates loss of renal function at least in proteinuric patients. Renin inhibitors on top of RAS blockade cause further reduction of proteinuria, but evidence for the effect on harder end-points is currently not (yet) available.
- *Beta-blockers*: in view of the highly elevated sympathetic activity in renal patients, it is rational to administer β -blockers, specifically those without metabolic side-effects (carvedilol, nebivolol), even in the absence of controlled evidence.
- *Mineralocorticoid receptor blockers*: there is good evidence that addition of spironolactone or eplerenone further reduces proteinuria in CKD patients in whom proteinuria is not adequately lowered by RAS blockade or increased after an initial decrease (so-called 'escape'). There are concerns with respect to hyperkalaemia, and appropriate controls of serum potassium are absolutely necessary.
- *Statins*: in patients with CKD, statins definitely reduce CV events, and some reduction of proteinuria is an added benefit. Evidence for their efficacy in patients on haemodialysis is currently not available, but at least in patients with CHD who are entering dialysis with statin therapy, statins should be continued independently of LDL cholesterol (which is often spuriously lowered because of the inflammatory state of uraemia).
- *Phosphate binders*: hyperphosphataemia (and elevated concentration of the phosphaturic hormone FGF23) are strong predictors of death in patients with CKD. Evidence for cardiovascular benefit from lowering phosphate is not (yet) strong, but lowering of phosphataemia to normal values by oral phosphate binders (calcium carbonate, lanthanum carbonate, sevelamer) or phosphate transport inhibitors (nicotinamide) is clearly indicated even in the absence of controlled data.
- *Vitamin D*: a great proportion of CKD patients have vitamin D deficiency (defined as 25(OH)D below 30 ng/mL); in this case, oral cholecalciferol should be administered; in observational studies, low 25(OH)D concentrations were also associated with an increased risk of CV events. Active vitamin D (1,25(OH)₂D₃) is synthesized in the kidney and its concentration decreases progressively and is specifically

low in end-stage kidney disease, triggering elevation of parathyroid hormone (PTH). Active vitamin D should be administered if the PTH concentration is above the recommended range (which is currently still under dispute).

- *Erythropoietin (EPO) and iron*: there is currently uncertainty about EPO treatment. Treatment is reasonable if haemoglobin values are less than 9 g/dL after adequate treatment of iron deficiency, if present.

See Fig. 13.1.

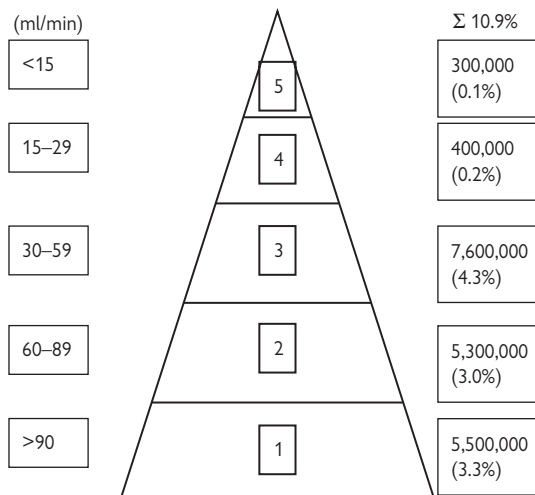


Fig. 13.1 Stages of chronic kidney disease: prevalence in the general population. Reproduced with permission from Levey, *American Journal of Kidney Disease*, (2002) **S1**: S1–S266.

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Cardiovascular disease in less-developed countries

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Burden of cardiovascular disease in less-developed countries

Approximately 80% of the world's people reside outside Western Europe and Canada/USA. Although cardiovascular diseases (CVD) occur throughout the world, their form and the burden change as a country undergoes economic development. Less-developed countries begin with a disease burden dominated by infectious, perinatal, and nutritional diseases and, in the process of development, make the transition to one dominated by non-communicable disease (NCD), particularly CVD. The four stages of transition are shown in Table 14.1.

Table 14.1 Deaths caused by cardiovascular disease at different stages of development¹

Stage of development	Deaths from CVD (% of total)	Predominant CVDs	Regional Examples
Age of pestilence and famine	5–10	Rheumatic heart disease, tuberculous pericarditis, and infectious and nutritional cardiomyopathies	Sub-Saharan Africa, rural India, and South America
Age of receding pandemics	10–35	As above, plus hypertensive heart disease, haemorrhagic stroke, and renal failure	China, urban South Africa
Age of degenerative and man-made diseases	35–55	All forms of stroke, ischaemic heart disease at relatively young ages	Urban India, formerly socialist economies
Age of delayed degenerative diseases	<50	Stroke and ischaemic heart disease at older ages	Western Europe, North America, Australia, New Zealand

Many less-developed countries have a triple burden of disease, encompassing disorders that characterize the first three phases of the epidemiologic transition.

In 2000, CVD accounted for 16.7 million deaths globally; 31% of all global deaths are due to CVD. Coronary heart disease (CHD) and stroke account for 71% of CVD deaths. Low- and middle-income countries contribute 78% of all CVD deaths, and 86% of disability-adjusted life years' (DALYs)' loss attributed to CVD. The relative importance of CHD and stroke varies across regions and countries. For example, more than twice

¹ Howson CP, Reddy KS, Ryan TJ, Bale JR (1998). *Control of Cardiovascular Diseases in Less Developed Countries: research, development, and institutional strengthening*. Washington DC: Institute of Medicine, National Academy Press.

as many deaths from stroke occur in the less developed countries as in developed countries.

NCDs rank first in most less-developed countries, in developed countries, and worldwide as a cause of death. CVD accounts for about half of all NCD deaths. In 1990, CVDs were the leading cause of death for all major geographic regions of the developing world except India and sub-Saharan Africa.




There is an early age of CVD deaths in less-developed countries compared to developed countries. In 1990, the proportion of CVD deaths occurring below the age of 70 years was 26.5% in developed countries, compared to 46.7% in less-developed countries. Therefore, the contribution of the less-developed countries to the global burden of CVD, in terms of DALYs lost, was nearly three times higher than that of developed countries.

Rheumatic heart disease (RHD) is the most common cause of CVD in children and young adults in less-developed countries. At least 15.6 million persons are estimated to be affected with RHD globally. More than 2 million require repeated hospitalization and 1 million will need heart surgery over the next 20 years. Annually, 233 000 deaths occur as a result of RHD. Many poor persons, who are preferentially affected, are disabled because of lack of access to the expensive medical and surgical care demanded by the disease. The prevalence of RHD in less-developed countries ranges from 20 to 40 per 1000 (by echocardiographic screening of schoolchildren). The incidence of rheumatic fever ranges from 13 to 374 per 100 000, and the rate of recurrence is high.

Managing with limited resources

The management of CVD is often technology intensive and expensive. Procedures for diagnosis or therapy, drugs, hospitalization, and frequent consultations with healthcare providers all contribute to the high cost. The high expenditure on tertiary care in most less-developed countries probably has a large contribution from CVD. This may divert scarce resources from developmental needs and from the unfinished agenda of infectious and nutritional disorders. Thus there is an urgent need for cost-effective preventive strategies and case-management approaches that are based on the best available evidence, and generalized to the context of each developing country.

Infectious disease and the heart

Numerous infectious diseases may involve the endocardium (see  Infective endocarditis, Chapter 4, pp. 187–209), myocardium (see  Heart muscle diseases, Chapter 8, pp. 417–457), and the pericardium (see  Pericardial diseases, Chapter 9, pp. 459–476). This section deals with a miscellaneous group of infectious diseases that are of particular relevance to cardiology practice outside Western Europe, e.g. human immunodeficiency virus (HIV) infection, Chagas' disease, diphtheria, syphilis, and tetanus. Although occasional examples have been reported, myocardial involvement is so rare as to be of little clinical significance in tuberculosis (apart from pericarditis), typhoid fever, scrub typhus, poliomyelitis, infective hepatitis, virus pneumonias, and other respiratory tract infections.

Diphtheria

Cardiac damage in diphtheria is due to a circulating exotoxin that inhibits protein synthesis in target tissues, with a high degree of affinity for the conduction system. Myocarditis occurs in up to 25% of cases of diphtheria and carries a mortality of approximately 60%.

Pathological examination shows a flabby dilated heart with a 'streaky' appearance of the myocardium. Microscopy reveals characteristic fatty infiltration of the myocytes, and other features of myocarditis.

Sinus tachycardia, gallop rhythm, cardiomegaly, and hypotension typically appear in the second week of illness.

The electrocardiogram (ECG) abnormalities are useful in diagnosis and fall under two headings:

- tracings showing evidence of diffuse myocardial damage: low voltage, prolongation of the QT interval, and T-wave flattening or inversion
- tracings showing evidence of damage to the conduction system with all degrees of atrioventricular (AV) block. The development of bundle branch block or complete heart block is a particularly ominous finding, and the reported mortality rates vary from 54% to 100% despite the insertion of transvenous pacing. The presence of myocardial damage is confirmed by marked elevation of the serum creatine kinase (CK) level; a high level is associated with poor prognosis.

The ECG eventually returns to normal but conduction abnormalities may persist for years.

Treatment

Treatment consists of supportive measures for heart failure, antibiotics (procaine penicillin G 600 000 U IM 12 hourly for 10 days or erythromycin 250–500 mg PO 6 hourly for 7 days) to prevent secondary infection and eliminate the diphtheria organisms in the throat, and temporary pacing in cases of AV heart block. Antitoxic serum should not be given at this stage because the exotoxin is already fixed and because of the risk of fatal serum reactions. Intubation and ventilation may be required for those patients with evidence of respiratory failure.

HIV and the cardiovascular system

The clinical effects of HIV on the heart are relatively uncommon, relative to the impact of HIV infection on the lungs, gastrointestinal tract, central nervous system, and skin. There are similarities in the pattern of CVD involvement in people living in developed and less-developed countries, but differences in the causative organisms implicated. The main presentations are (1) pericardial effusion; (2) cardiomyopathy; (3) pulmonary hypertension; (4) large vessel aneurysms; and (5) metabolic complications associated with anti-retroviral drug use.

Pericardial effusion

Pericardial effusion is one of the early presenting features of HIV infection in patients living in sub-Saharan Africa. Whereas in western countries, a large effusion is usually idiopathic in 80% of patients with acquired immune deficiency syndrome (AIDS), the disease is caused by tuberculosis in over 80% of Africans living with HIV. Purulent pericarditis is not uncommon, while involvement with Kaposi's sarcoma and B-cell lymphoma is rare. Treatment of tuberculous pericarditis is with a standard anti-tuberculous regime similar to that used in HIV-negative patients, and the short-term outcome is similar. The role of adjuvant steroids is uncertain.

Cardiomyopathy

Cardiomyopathy is found in 50% of acutely ill hospitalized patients, and in 15% of ambulatory asymptomatic patients living with HIV. Myocarditis is present in a proportion of the cases. In western series, the myocarditis is associated with cardiotropic virus, whereas in Africa, preliminary data suggest that it may be associated with non-viral opportunistic infections such as toxoplasmosis, cryptococcosis, and *Mycobacterium avium intracellulare* infection. HIV-positive patients with cardiomyopathy should be considered for endomyocardial biopsy to exclude a treatable cause of myocarditis. Otherwise, treat as for heart failure. Prognosis is poor, with a median survival of 100 days without anti-retroviral drugs.

Pulmonary hypertension

HIV-associated pulmonary hypertension is estimated to be 1/200, much higher than the 1/200 000 found in the general population. Primary pulmonary hypertension is found in 0.5% of hospitalized AIDS patients and is a cause of cor pulmonale and death. The pathogenesis is poorly understood.

Arterial aneurysm

HIV-related arterial aneurysm is a distinct clinical and pathological entity that is associated with advanced HIV disease. HIV-related aneurysms affect young patients (median age 30 years) with no risk factors for atherosclerosis, occur mainly in peripheral arteries (carotid, distal superficial femoral, and popliteal sites), are usually multiple (1–10 per patient), and have been reported more frequently in black patients than in white individuals. The inflammatory process involves the *vasa vasorum* of the adventitia with sparing of the media and intima. The most frequent mode of presentation is that of a painful mass of increasing size. The diagnosis is confirmed by

duplex sonography or computed tomography (CT). Arterial angiography is performed to delineate the extent of aneurysm. Serological testing for syphilis, typhoid, HIV, and autoimmune disease is indicated. Treatment is by operative intervention for symptomatic aneurysm in patients with an acceptable surgical risk and anticipated life expectancy.

Metabolic abnormalities

The use of protease inhibitors and nucleoside reverse transcriptase inhibitors is associated with the following metabolic abnormalities: fat redistribution (lipodystrophy), increased total cholesterol and triglycerides, decrease in high-density lipoprotein (HDL), impaired glucose tolerance, and increased intra-abdominal fat. These changes translate into a small increase in the risk of myocardial infarction (MI) with the long-term use of anti-retroviral drugs. It is prudent to modify cardiovascular risk factors and treat the metabolic complications when they arise, according to standard guidelines in affected patients.

Chagas' disease and the heart

Chagas' disease is a myocarditis of parasitic origin that is caused by the protozoa *Trypanosoma cruzi*. The disease is a major public health problem in South and Central America; 15–18 million people are infected with the parasite, and 65 million people are at risk. Chagas' disease is transmitted by contamination of the bite wound of the 'assassin' or 'kissing' reduviid bugs with the infected faeces of the insect.

Natural history

The natural history of Chagas' disease is characterized by three phases: acute, latent, and chronic. *Acute Chagas' disease* occurs predominantly in children in less than 10% of infected cases; it is fatal in 10% of cases. It is characterized by fever, lymphadenopathy, hepatosplenomegaly, and facial oedema. Acute myocarditis is common and may be fatal. Rarely, meningoencephalitis or convulsive seizures may occur, sometimes causing permanent mental or physical defects or death. Recovery is usual, however, and the disease is quiescent for the next 10 to 15 years (*latent Chagas' disease*). *Chronic Chagas' disease* may be asymptomatic, mild, or accompanied by cardiomyopathy, megaesophagus, and megacolon, with a fatal outcome. The late manifestations probably result from lymphocyte-mediated destruction of muscle tissue and nerve ganglions during the acute stage of the disease. *Trypanosoma cruzi* may be found in degenerated muscle cells, especially in the right atrium.

The disease is characterized clinically by anginal chest pain, symptomatic conduction system disease; severe, protracted, congestive cardiac failure, often predominantly right sided, is the rule in advanced cases. Bifascicular block is present in more than 80% of cases and death from asystole and arrhythmia is common. Autonomic dysfunction is common. Apical aneurysms and left ventricular dilatation increase the risk of thromboembolism and arrhythmias.

Diagnosis

Chagas' disease is identified by demonstration of trypanosomes in the peripheral blood or leishmanial forms in a lymph node biopsy, or by animal inoculation or culture, xenodiagnosis (i.e. the patient is bitten by reduviid bugs bred in the laboratory; the subsequent identification of parasites in the intestine of the insect is proof of infection in the human host), or serologic tests (e.g. Machado–Guerreiro complement fixation test). The chest X-ray (CXR) demonstrates cardiomegaly. The ECG is abnormal as a rule in the late course of the disease. The echocardiographic features in advanced cases are those of dilated cardiomyopathy; a left ventricular posterior wall hypokinesis and relatively preserved interventricular septum motion, associated with an apical aneurysm is distinctive. Radionuclide ventriculography may show ventricular wall motion abnormality in the absence of overall depression of global ventricular function. Perfusion scanning with thallium-201 may show fixed defects (corresponding to areas of fibrosis) as well as evidence of reversible ischaemia. Gadolinium-contrast magnetic resonance imaging (MRI) can identify patients with more active myocardial disease.

Treatment

There is no specific therapy for Chagas' disease. Prolonged administration of nifurtimox, a nitrofurazone derivative, may effect parasitologic cure, but chronic organ damage is irreversible. Heart failure, arrhythmias, and thromboembolism are treated with the usual measures.

Prevention

Reduviid bugs, the vectors for Chagas' disease, inhabit poorly constructed houses and outbuildings. Spraying with 5% γ -benzene hexachloride is most effective in controlling the vector. Patching wall cracks and cementing over dirt floors also helps to eliminate the vectors.

Cardiovascular syphilis

Cardiovascular syphilis produces thoracic aneurysm, narrowing of the coronary ostia, or aortic valvular insufficiency that usually appears 10 to 25 years after the initial infection. Involvement of the myocardium is rare. The introduction of penicillin has made the disease less common, but it remains an important cause of CVD in poor populations.

Coronary disease

Angina pectoris, rarely MI, cardiac aneurysm, or sudden death may result from involvement of the coronary ostia. Aortic insufficiency is nearly always present. The condition should be suspected when angina pectoris is encountered in young men, and when severe angina is associated with disproportionately mild aortic insufficiency. Glyceryl trinitrate is often less effective in relieving symptoms. Attacks of angina decubitus are not infrequent. The diagnosis is established by positive syphilis serology and coronary angiography. Successful surgical treatment may be achieved by endarterectomy of the coronary ostia or by bypass grafting.

Aortic insufficiency

The presenting symptoms may be those of coronary insufficiency or of left heart failure. The physical signs are the same as those of rheumatic aortic insufficiency. Pure insufficiency without any stenosis is the rule. Because of the unfolding and dilatation of the aorta, the murmurs are frequently better heard to the right of the sternum. Occasionally, a musical ('cooing-dove') diastolic murmur is produced by eversion or detachment of an aortic cusp.

Syphilitic aortic aneurysm

This involves the ascending aorta and the arch with equal frequency. Less commonly, the descending aorta is involved, and least commonly the abdominal aorta. It is not unusual for the aorta to be involved at more than one site in the same patient. Syphilitic aneurysms are usually saccular (vs. fusiform aneurysms of atherosclerosis). Syphilitic aneurysms can rupture, but never dissect. The clinical presentation is dependent on compression of adjacent structures and therefore varies with the portion of the aorta involved.

Ascending aorta aneurysms have been termed the 'aneurysms of signs':

- compression of the superior vena cava (SVC)—distended non-pulsatile neck veins with oedema in their drainage area
- compression of the right main bronchus—lung complications
- compression of the right ventricular outflow tract (RVOT)—signs of pulmonary stenosis
- erosion of the sternum—superficial pulsating mass.

Aortic arch aneurysms are known as the 'aneurysms of symptoms':

- large airway compression—dry 'brassy' cough, dyspnoea
- recurrent laryngeal nerve compression—hoarseness
- oesophageal compression—dysphagia
- compression of the sympathetic chain—Horner's syndrome
- erosion of the vertebrae and compression of nerves—deep-seated continuous bone and root pain.

An aneurysm may be suspected clinically by unequal pulses and blood pressures in the upper limbs or by the presence of a tracheal tug. Not infrequently, an aneurysm is first detected by CXR, and must be distinguished from other masses. Linear calcification of the aneurysmal sac and expansile pulsation on fluoroscopy are helpful signs when present. Aortic angiography is required for diagnosis.

Treatment

Benzathine penicillin G should be given in doses of 2.4 million units weekly for three successive weeks. When there is penicillin allergy, tetracycline 500 mg four times per day for 1 month may be administered.

Beri-beri (thiamine deficiency)

The coenzyme thiamine pyrophosphate (TPP) participates in carbohydrate metabolism through decarboxylation of α -keto acids. Thiamine also acts as a coenzyme to the apoenzyme transketolase in the pentose monophosphate pathway for glucose. Thiamine deficiency may produce dry or wet beri-beri. Dry beri-beri manifests with peripheral neurologic and cerebral disturbances. The wet form is associated with cardiovascular manifestations.

Aetiology

Primary thiamine deficiency arises from inadequate intake, particularly in people subsisting on highly polished rice (e.g. in the Far East). Milling removes the husk, which contains most of the thiamine.

Secondary thiamine deficiency arises from (1) increased requirement, as in hyperthyroidism, pregnancy, lactation, and fever; (2) impaired absorption, as in long-continued diarrhoea; (3) impaired utilization, as in severe liver disease; and (4) increased urinary excretion, as in chronic furosemide therapy. A combination of decreased intake, impaired absorption and utilization, increased requirements, and possibly apoenzyme defect occurs in alcoholism. Highly concentrated dextrose infusions, coupled with low thiamine intake, may precipitate thiamine deficiency.

Cardiovascular (wet) beri-beri

Cardiovascular (wet) beri-beri takes 2 forms—the more common high-output state or the rare low-output state (*Shoshin disease*). In the former, before heart failure supervenes, there is tachycardia, a wide pulse pressure, sweating, and a warm skin. With heart failure, orthopnoea, pulmonary and peripheral oedema, and peripheral vasoconstriction causing cold and cyanosed extremities occur. Severe hypotension, lactic acidosis, very low systemic vascular resistance, and absence of oedema characterize the low-output state (*Shoshin disease*). In the latter, death occurs within a few hours or days, unless appropriate treatment is given. Even after several episodes of cardiovascular beri-beri, permanent myocardial damage is extremely rare.

Infantile beri-beri

Infantile beri-beri occurs in infants breast-fed by thiamine-deficient mothers, usually between the 2nd and 4th month of life. Cardiac failure, aphonia, and absent deep tendon reflexes are characteristic.

Clinical features

The diagnosis of beri-beri should always be considered in any case of heart failure in an alcoholic where the cause is not readily apparent. Neurologic symptoms such as paraesthesiae and weakness because of peripheral neuropathy, and Wernicke's encephalopathy are occasionally present.

Signs of a hyperkinetic circulatory state are manifested by warm hands, tachycardia, collapsing pulses, and raised jugular venous pressure (JVP). A wide pulse pressure with systolic hypertension is commonly found, but occasionally diastolic hypertension is also present initially, so that hypertensive

heart failure may be suspected. The heart is almost invariably enlarged, with a gallop rhythm. Atrioventricular regurgitant murmurs may be present, and tricuspid insufficiency is particularly common. Occasionally, right-sided heart failure dominates the clinical picture and there is disproportionate oedema and hepatomegaly. In Shoshin beri-beri, there is severe heart failure with low cardiac output, orthopnoea, systemic congestion, and oliguria.

The ECG findings are of crucial value in diagnosis. The most common finding is a normal tracing, or one demonstrating right-axis deviation with clockwise rotation, when the patient is most severely ill. Less commonly, the initial ECG shows T-wave inversion over the left or right ventricular precordial leads. In either event, daily tracings will show serial changes, over either the right ventricle or left ventricle, or both. Thus, when the patient has apparently recovered completely, the ECG may actually be at its worst, showing expansive and deep T-wave inversion. The abnormal changes may persist for 24 hours, days, or even weeks following recovery, but complete return to normal is the rule.

CXR: Radiologically, equally striking serial changes occur. Marked cardiomegaly with a prominent right ventricular outflow and hilar congestion rapidly returns to normal in a week or two following appropriate treatment.

Laboratory findings: Erythrocyte transketolase activity is diminished before and increases after the addition of thiamine pyrophosphate (TPP effect); a TPP effect >15% suggests thiamine deficiency. The blood sample must be taken in a heparin-coated vial, before administration of thiamine, and transported to the laboratory on ice. Elevated blood pyruvate and lactate, and diminished urinary thiamine excretion (<50 µg/day) are also found.

Treatment

Treatment is with thiamine 50–100 mg IV or IM immediately, and repeated daily for 1–2 weeks. The response to thiamine is usually prompt and complete. Marked diuresis, decrease in heart rate and size, and clearing of pulmonary congestion may occur in 12 to 48 hours. However, sudden death from pulmonary oedema may occur, so that it is prudent to treat with digitalis and diuretics at the outset.

Tetanus

Tetanus is caused by the endotoxin (tetanospasmin) from the anaerobic organism *Clostridium tetani*. The portal of entry is usually a severe or untreated wound, often a neglected burn or, occasionally, a septic incomplete abortion. In a few cases (15–30%), the portal of entry is never isolated. Public health immunization programmes with tetanus toxoid have dramatically reduced the incidence of neonatal tetanus in many parts of the world, but there is still a significant number of cases in adults.

Features of special importance in the history are the period from injury to onset of symptoms and the time interval between the onset of stiffness to the onset of spasms. In general, the shorter the period from injury to onset of symptoms and the shorter the time interval between symptoms and spasms, the more severe the tetanus will be.

The most useful classification of tetanus is simply:

- *mild*—stiffness and mild spasms
- *moderate*—stiffness and/or spasms with dysphagia
- *severe*—severe recurrent spasms and dysphagia ± autonomic overactivity.

Sympathetic overactivity remains the major cause of death in patients with tetanus once early deaths from respiratory obstruction and the deaths from mechanical failure have been eliminated. The syndrome of sympathetic overactivity results in tachycardia, marked fluctuation of blood pressure (i.e. both hypotensive and hypertensive changes), excessive salivation, and sweating. This fluid loss may result in dehydration. The effect on the heart can give rise to MI.

A treatment approach that involves the use of extremely heavy sedation with intermittent positive pressure ventilation has proven to be successful in reducing mortality to 6% in the authors' practice.

Keshan disease

Selenium is involved in the reoxidation of reduced glutathione and has close metabolic interrelationships with vitamin E. It is part of the enzyme glutathione peroxidase, which is thought to destroy peroxides derived from unsaturated fatty acids. Deficiency has occurred in patients on long-term parenteral feeding. Several cases of fatal cardiomyopathy have been attributed to selenium deficiency. In China, a childhood cardiomyopathy known as Keshan disease, after the province in which it has been studied, has been attributed to selenium deficiency and protection claimed for prophylactic dosing with 150 µg selenium/day as selenomethionine. Selenium levels have also been found to be low in some patients with HIV-associated cardiomyopathy, with a response to selenium supplementation.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (which is discussed elsewhere in this book) is divided into a diffuse *non-obliterative* variety (e.g. amyloidosis, haemochromatosis) and an *obliterative* variety in which the endocardium and subendocardium are fibrosed (e.g. endomyocardial fibrosis). Variants of restrictive obliterative cardiomyopathy occur in temperate zones, described as *Loeffler endocarditis*, and in the tropical rainforest regions as *endomyocardial fibrosis (EMF)*. Tropical EMF affects children in very low socio-economic groups; it is not restricted to specific racial groups, as Europeans living in the tropics have also been affected.

It has been suggested that Loeffler endocarditis and tropical EMF are part of a continuum of the same disease, commencing with hypereosinophilia of whatever cause, resulting in myocardial damage in three stages: a *necrotic phase* (eosinophilic myocarditis with arteritis i.e. Loeffler endocarditis) for the first few months of illness; a *thrombotic phase* with early thickening of the myocardium with thrombosis after about 1 year of presentation; and the *late stage* of fibrosis (i.e. EMF). However, there are differences in the clinical presentation of tropical EMF and Loeffler endocarditis: i.e. geographic, age (Loeffler endocarditis affects middle-aged men vs. tropical EMF which affects young people and children), pattern of ventricular involvement (tropical EMF affects mainly right ventricle vs. Loeffler endocarditis affects either ventricle), and link with eosinophilia (Loeffler is associated with hypereosinophilia vs. link of tropical EMF with eosinophilia, which has not been established).

Endomyocardial fibrosis

Pathophysiology

Fibrous tissue and the chordae adherent to the ventricular wall may bind down the papillary muscle. In the extreme stage, when there is obliterative cardiomyopathy, the cavity of the ventricle is occupied entirely by fibrous tissue and superimposed thrombus. The disease may involve either or both ventricles and be complicated by pericarditis, with effusion and high diastolic pressure giving rise to pulmonary and systemic venous congestion with AV valve incompetence.

Symptoms and signs

Typically, symptoms are suggestive of congestive cardiomyopathy, but signs resemble constrictive pericarditis. Like congestive cardiomyopathy, patients present with dyspnoea, orthopnoea, and peripheral oedema. Like constrictive pericarditis, pulsus paradoxus, a raised JVP with rapid 'x' and 'y' descents, an early third heart sound, hepatomegaly, and ascites are present. In contradistinction to constrictive pericarditis, however, there is frequently a murmur of tricuspid and/or mitral regurgitation. Chronic, severe tricuspid regurgitation that is often seen in right-sided endomyocardial fibrosis may cause bilateral proptosis.

Diagnosis

ECG is usually non-specifically abnormal, showing low-voltage QRS complexes and ST-T wave abnormalities, and may indicate right atrial enlargement in the form of tall peaked P waves. CXR may demonstrate an enlarged cardiac silhouette similar to a pericardial effusion. *Echocardiography* shows increased ventricular wall thickness cavity obliteration, and enlarged atria, with or without a small pericardial effusion. *Cardiac catheterization* demonstrates the combination of restricted filling and incompetence of the AV valves. The right atrial pressure is elevated, with prominent systolic waves and steep 'x' and 'y' descents. In severe obliterative cases, the pressures in the right atrium, right ventricle, and pulmonary arteries may be identical, and an *intracardiac ECG* may be required to locate the position of the tricuspid and pulmonary valves. A dip and plateau ('square root') type of pressure pulse is frequently present in both ventricles. *Ventriculography* shows an enormously dilated right atrium and obliteration of the right ventricular apex. Endomyocardial biopsy of the right ventricle may be useful, by demonstrating an excess fibrous tissue, a finding that is highly suggestive of endomyocardial fibrosis. The distinguishing clinical, echocardiographic, and haemodynamic features between restrictive cardiomyopathy and constrictive pericarditis are discussed under the section on constrictive pericarditis. However, in those forms of this syndrome where significant cardiomegaly is absent, a distinction from constrictive pericarditis may be impossible. The only means of making a diagnosis is then *exploratory thoracotomy*.

Prognosis and treatment

There is no specific treatment for endomyocardial fibrosis, and prognosis is poor (35–50% 2-year mortality). *Diuretics* must be used with caution because of their ability to lower the preload upon which the non-compliant ventricles depend to maintain cardiac output. *Digitalis* is helpful in patients with atrial fibrillation. Afterload reducers may induce profound hypotension, and are usually of no value. Operative excision of the fibrotic endocardium (*endocardial resection*) and replacement of one or both AV valves may lead to symptomatic improvement, but is associated with a high peri-operative mortality (15–25%) and no survival benefit. *Cardiac transplantation* is the definitive treatment for EMF.

Loeffler endocarditis

Marked eosinophilia of any cause may be associated with endomyocardial disease. but the cause of eosinophilia in most patients with Loeffler endocarditis is unknown. The typical patient is a man in his 4th decade who lives in a temperate climate and has the hypereosinophilic syndrome (i.e. persistent eosinophilia with ≥ 1500 eosinophils/mm³ for at least 6 months or until death, with organ involvement).


Pathology

Multi-organ disease involving the heart, lungs, bone marrow, and brain. Cardiac involvement is often biventricular, with mural endocardial thickening of the inflow portions and apex of ventricles. There are histological features of eosinophilic myocarditis, mural thrombosis, and fibrotic thickening of the endocardium.

Symptoms and signs

Constitutional symptoms (fever, weight loss), cough, and rash. Overt symptoms and signs of congestive heart failure are found in 50% of patients. Cardiomegaly and the murmur of mitral regurgitation may be found even in patients without cardiac symptoms. Systemic embolism is frequent. Death is usually due to cardiac failure, often associated with renal, hepatic or respiratory failure.

Diagnosis

EKG most commonly shows non-specific ST-T-wave changes, but atrial fibrillation and right bundle branch block are common. CXR may reveal cardiomegaly and pulmonary congestion or pulmonary infiltrates. Echocardiogram shows localized thickening of the posterobasal left ventricular wall, with limited or absent motion of the posterior leaflet of the mitral valve; enlarged atria, atrioventricular valve regurgitation; and usually preserved systolic function. Cardiac catheterization reveals the haemodynamic features of a restrictive cardiomyopathy which are indistinguishable from tropical EMF outlined in  Restrictive cardiomyopathy, p. 667. The diagnosis is often confirmed by endomyocardial biopsy.

Management

Medical therapy during the course of Loeffler endocarditis and surgical therapy during later phases of fibrosis may have a positive effect on symptoms and survival. Corticosteroids are indicated for acute myocarditis, and together with hydroxyurea may improve survival. Some non-responders have responded to interferon. Routine cardiac therapies with diuretics, digitalis, afterload reduction, and anticoagulation are important adjuncts. Surgical therapy offers palliation of symptoms once the fibrotic stage has been reached.

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Basic principles

Cardiac disease in pregnancy is rare in the UK, Europe, and the developed world, but common in developing countries. In the UK, rheumatic heart disease is now extremely rare in women of childbearing age and is confined to immigrants. Women with congenital heart disease, having undergone corrective or palliative surgery in childhood, survive into adulthood, and are encountered more frequently. These women may have complicated pregnancies. Women with metal prosthetic valves face difficult decisions regarding anticoagulation in pregnancy. Ischaemic heart disease (IHD) is becoming more common in pregnancy, as the mean age of pregnancy increases and the smoking epidemic continues. Dissection of the aorta and its branches occurs more commonly in pregnancy, and pregnancy may cause a specific dilated cardiomyopathy—peripartum cardiomyopathy.

Despite its relative rarity, cardiac disease is the leading cause of maternal death in the UK, being responsible for 48 deaths in the three years 2003–2005 inclusive.¹ The predominant cardiac causes of maternal death in the UK are peripartum cardiomyopathy, myocardial infarction (MI), and dissection of the aorta and its branches.

Because of significant physiological changes in pregnancy, symptoms such as palpitations, and signs such as an ejection systolic murmur are very common and innocent findings. The care of the pregnant and parturient woman with heart disease requires a multidisciplinary approach and formulation of an agreed and documented management plan encompassing management of both planned and emergency delivery.

This chapter will cover the most important cardiac conditions relevant to pregnancy.

¹ Nelson-Piercy C (2007). Cardiac disease. In: Lewis G (ed). *The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the UK*. London: CEMACH.

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Physiological changes in pregnancy

Cardiac output increases early in pregnancy, reaching a maximum by the mid-second trimester. This is achieved by an increase in both stroke volume and heart rate. There is peripheral vasodilation, and a fall in systemic and pulmonary vascular resistance.

Although there is no increase in pulmonary capillary wedge pressure (PCWP), serum colloid osmotic pressure is reduced. The colloid oncotic pressure–PCWP gradient is reduced by 28%, making pregnant women particularly susceptible to pulmonary oedema. Pulmonary oedema will be precipitated if there is either an increase in cardiac preload (such as infusion of fluids), or increased pulmonary capillary permeability (such as in pre-eclampsia), or both.

In late pregnancy, in the supine position, pressure of the gravid uterus on the inferior vena cava (IVC) causes a reduction in venous return to the heart and a consequent fall in stroke volume and cardiac output. Turning from the lateral to the supine position may result in a 25% reduction in cardiac output. Pregnant women should therefore be nursed in the left or right lateral position wherever possible. If the mother has to be kept on her back, the pelvis should be rotated so that the uterus drops forward, and cardiac output as well as uteroplacental blood flow are optimized. Reduced cardiac output is associated with reduction in uterine blood flow and therefore in placental perfusion; this can compromise the fetus.

Labour is associated with further increases in cardiac output (15% in the first stage and 50% in the second stage). Uterine contractions lead to auto transfusion of 300–500 mL of blood back into the circulation, and the sympathetic response to pain and anxiety further elevates heart rate and blood pressure. Cardiac output is increased more during contractions but also between contractions.

Following delivery, there is an immediate rise in cardiac output due to the relief of IVC obstruction, and contraction of the uterus that empties blood into the systemic circulation. Cardiac output increases by 60–80%, followed by a rapid decline to pre-labour values within about one hour of delivery. Transfer of fluid from the extravascular space increases venous return and stroke volume further. Those women with cardiovascular compromise are therefore most at risk of pulmonary oedema during the second stage of labour and the immediate post-partum period.

See Fig. 15.1.

Physiological changes in the cardiovascular system in pregnancy

Cardiac output	↑ 40%
Stroke volume	↑
Heart rate	↑ 10–20 beats per minute
Blood pressure	↓ First and second trimester → Third trimester
Central venous pressure	→
Pulmonary capillary wedge pressure (PCWP)	→
Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR)	↓ 25–30%
Serum colloid osmotic pressure	↓ 10–15%

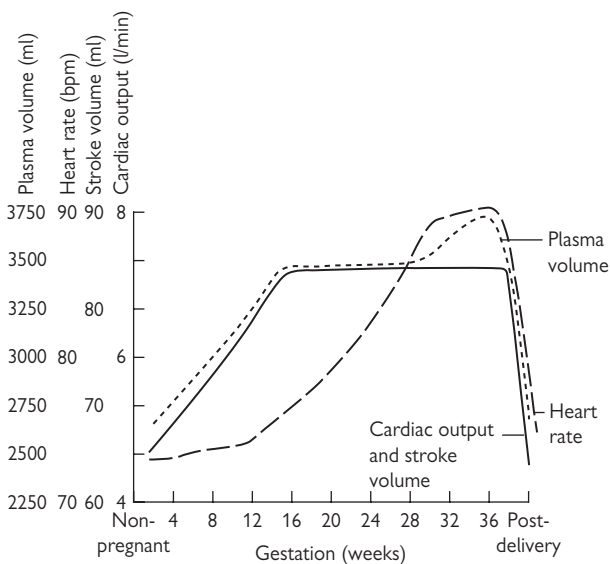


Fig. 15.1 Physiological changes in pregnancy. Systemic and pulmonary vascular resistance fall during pregnancy. Blood pressure may fall in the second trimester, rising slightly in late pregnancy. Note the cardiac output and stroke volume peak by 16 weeks' gestation. Reproduced with permission from Thorne SA (2004). Pregnancy in heart disease. *Heart* **90**: 450–6.

Normal findings in pregnancy

On examination

Findings may include:

- bounding/collapsing pulse
- ejection systolic murmur (present in over 90% pregnant women; may be quite loud, and audible all over the praecordium)
- third heart sound
- relative sinus tachycardia
- ectopics
- peripheral oedema.

On electrocardiography (ECG)

These are partly related to changes in the position of the heart:

- atrial and ventricular ectopics
- Q wave (small) and inverted T wave in lead III
- ST-segment depression and T-wave inversion inferior and lateral leads
- QRS axis leftward shift.

Investigations

- The amount of radiation received by the fetus during a maternal chest X-ray (CXR) is negligible and CXRs should never be withheld if clinically indicated in pregnancy.
- Transthoracic and transoesophageal echocardiograms are also safe, with the usual precautions to avoid aspiration.
- Magnetic resonance imaging (MRI) is safe in pregnancy.
- Routine investigation with electrophysiological studies and angiography is normally postponed until after pregnancy but should not be withheld in, for example, acute coronary syndromes.

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General considerations in pregnancy

The heart has relatively less reserve than the respiratory system. Women with heart disease may not be able to increase their cardiac output adequately to cope with pregnancy and delivery.

The outcome and safety of pregnancy are related to the:

- presence and severity of pulmonary hypertension
- presence of cyanosis
- haemodynamic significance of the lesion
- functional class as determined by the level of activity that leads to dyspnoea (New York Heart Association, NYHA).¹

Cardiac events such as stroke, arrhythmia, pulmonary oedema, and death complicating pregnancies are predicted by:²

- a prior cardiac event or arrhythmia
- NYHA classification >II
- cyanosis
- left ventricular ejection fraction (LVEF) <40%
- left heart obstruction (mitral valve area <2 cm², aortic valve area <1.5 cm², aortic valve gradient >30 mmHg).

Women with congenital heart disease are at increased risk of having a baby with congenital heart disease, and should therefore be offered detailed scanning for fetal cardiac anomalies.

Women with cyanosis (oxygen saturation <80–85%) have an increased risk of fetal growth restriction, fetal loss, and thromboembolism secondary to the reactive polycythaemia. Their chance of a live birth in one study was less than 20%.³

Women with the above risk factors for adverse cardiac or obstetric events should be managed and counselled by a multidisciplinary team, including cardiologists with expertise in pregnancy, obstetricians, fetal medicine specialists, and paediatricians. Regular antenatal visits and judicious monitoring to avoid or treat expediently any anaemia or infection or cardiac decompensation are essential. There should be early involvement of obstetric anaesthetists and a carefully documented plan for delivery.

1 McCaffrey FM, Sherman FS (1995). Pregnancy and congenital heart disease: The Magee Women's Hospital. *J Mat Fet Med* **4**: 152–9.

2 Siu SC, Sermer M, Colman JM, et al. (2001). Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* **104**: 515–21.

3 Presbitero P, Somerville J, Stone S, et al. (1994). Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. *Circulation* **89**: 2673–6.

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Pulmonary hypertension and pregnancy

Pulmonary vascular disease, whether secondary to a reversed large left-to-right shunt such as a ventral septal defect (VSD; Eisenmenger's syndrome) or to lung or connective tissue disease (e.g. scleroderma), or due to primary pulmonary hypertension, is extremely dangerous in pregnancy. Women known to have pulmonary vascular disease should be advised from an early age to avoid pregnancy and be given appropriate contraceptive advice. Maternal mortality is 25–40%.^{1,2} Most fatalities occur in the early puerperium. The danger relates to fixed pulmonary vascular resistance and an inability to increase pulmonary blood flow with refractory hypoxaemia. Most deaths can be attributed to thromboembolism, hypovolaemia or pre-eclampsia.

Pulmonary hypertension is defined as a non-pregnant elevation of mean (not systolic) pulmonary artery pressure equal to or greater than 25 mmHg at rest or 30 mmHg on exercise in the absence of a left-to-right shunt. Pulmonary artery systolic (not mean) pressure is usually estimated by using Doppler ultrasound to measure the regurgitant jet velocity across the tricuspid valve. This should be considered a screening test. There is no agreed relation between the mean pulmonary pressure and the estimated systolic pulmonary pressure. If the systolic pulmonary pressure estimated by Doppler is thought to indicate pulmonary hypertension, a specialist cardiac opinion is recommended. If there is pulmonary hypertension in the presence of a left-to-right shunt, the diagnosis of pulmonary vascular disease is particularly difficult and further investigation including cardiac catheterization to calculate PVR is likely to be necessary. Pulmonary hypertension as defined by Doppler studies may also occur in mitral stenosis and with large left to right shunts that have not reversed and, although such women may not have pulmonary vascular disease and a fixed PVR (or this may not have been established prior to pregnancy), they have the potential to develop it, and require very careful monitoring with serial echocardiograms.

Management

- In the event of unplanned pregnancy, a therapeutic termination should be offered.³ Elective termination carries a 7% risk of mortality, hence the importance of avoiding pregnancy if possible.
- If such advice is declined, multidisciplinary care, elective admission for bed rest, oxygen, and thromboprophylaxis are recommended. Therapies such as sildenafil and bosentan should be continued if they have led to reductions in pulmonary pressures, even though the latter is teratogenic in animals.
- There is no evidence that abdominal or vaginal delivery or regional versus general anaesthesia improve outcome in pregnant women with pulmonary hypertension.

1 Yentis SM, Steer PJ, Plaat F (1998). Eisenmenger's syndrome in pregnancy: maternal and fetal mortality in the 1990s. *Br J Obstet Gynaecol* **105**: 921–2.

2 Bédard E, Dimopoulos K, Gatzoulis MA (2009). Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* **30**: 256–65.

3 Thorne SA, Nelson-Piercy C, MacGregor A (2006). Risks of contraception and pregnancy in heart disease. *Heart* **92**: 1520–5.

Marfan syndrome and pregnancy

Eighty per cent of Marfan patients have some cardiac involvement, most commonly mitral valve prolapse and regurgitation. Pregnancy increases the risk of aortic rupture or dissection, usually in the third trimester or early post-partum. Progressive aortic root dilation and an aortic root dimension >4 cm are associated with increased risk (10%).¹ Those with aortic roots >4.6 cm should be advised to delay pregnancy until after aortic root repair.² Conversely, in women with minimal cardiac involvement and an aortic root <4 cm, pregnancy outcome is usually good,² although those with a family history of aortic dissection or sudden death are also at increased risk.

Management

- Monthly echocardiograms.
- β -blockers for those with hypertension or aortic root dilation.
- Vaginal delivery for those with stable aortic root measurements but elective caesarean section with regional anaesthesia if there is an enlarged or dilating aortic root.^{1,2}

1 Immer FF, Bansi AG, Immer-Bansi AS, et al. (2003). Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* **76**: 309–14.

2 Lipscomb KJ, Clayton Smith J, Clarke B, et al. (1997). Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* **104**: 201–6.

Valvular heart disease in pregnancy

Valvular heart disease affects ~1% of pregnancies and may be associated with an increased risk of adverse maternal, fetal, and neonatal outcomes. High-risk features include:

- impaired left ventricular (LV) function (ejection fraction (EF) < 40%)
- left-sided valve stenoses¹ (aortic stenosis (AS) with valve area < 1.5 cm² or mitral stenosis (MS) with valve area < 2.0 cm²)
- previous maternal cardiovascular system (CVS) event (congestive cardiac failure (CCF), transient ischaemic attack (TIA), cerebrovascular accident (CVA)), or
- symptoms* (NYHA class II or higher).

Risk increases with each additive factor, see box opposite.

* Associated with neonatal complications (preterm delivery, respiratory distress, fetal growth retardation (FGR), intraventricular haemorrhage, death).

Classification of valvular heart disease risk in pregnancy

Low maternal and fetal risk

- Asymptomatic AS with mean gradient <50 mmHg and normal LV function
- Aortic regurgitation (AR), NYHA class I/II and normal LV function
- Mitral regurgitation (MR), NYHA class I/II and normal LV
- MV prolapse with no MR or with mild–moderate MR and normal LV
- Mild–moderate mitral stenosis (MS) (mitral valve (MV) area >1.5 cm², gradient <5 mmHg), no severe pulmonary hypertension
- Mild–moderate pulmonic stenosis (PS)

High maternal and fetal risk

- Severe AS with or without symptoms
- AR and NYHA class III or IV symptoms
- MS with NYHA class II or higher
- MR with NYHA class III or IV symptoms
- Aortic valve (AV) disease, MV disease, or both, resulting in severe pulmonary hypertension (pulmonary artery (PA) pressure >75% systemic pressure)
- AV disease, MV disease, or both, with LV dysfunction (LVEF<40%)
- Maternal cyanosis
- Reduced functional status (NYHA class III or IV)

High maternal risk

- Impaired LV systolic function (LVEF <40%)
- Previous heart failure
- Previous CVA or TIA

High neonatal risk

- Maternal age <20 or >35 years
- Use of warfarin therapy throughout pregnancy
- Smoking during pregnancy
- Multiple gestations

Adapted from Reimold SC, Rutherford JD (2003). Valvular heart disease in pregnancy. *N Engl J Med* 349: 52–9, with permission.

Mitral stenosis and pregnancy

This is important in pregnancy because although asymptomatic at pregnancy onset, women may deteriorate secondary to tachycardia, arrhythmias, or the increased cardiac output. The commonest complication is pulmonary oedema secondary to increased left atrial pressure, and precipitated by increased heart rate or increased volume (such as occurs during the third stage of labour or following injudicious intravenous fluid therapy).¹ The risk is increased with severe MS (MV area $<1 \text{ cm}^2$), moderate or severe symptoms prior to pregnancy, and in those diagnosed late in pregnancy.¹

Management

- Women with severe MS should be advised to delay pregnancy until after valvotomy, or, if the valve is not amenable to valvotomy, until after MV replacement.
- β -blockers decrease heart rate, increase diastolic filling time,² and decrease the risk of pulmonary oedema.¹
- Diuretics should be continued in pregnancy.
- If medical therapy fails, or for those with severe MS, balloon mitral valvotomy may be safely and successfully used in pregnancy if the valve is suitable.^{1,2} Percutaneous balloon valvotomy carries a risk of major complications of about 1%, whereas for surgical valvotomy the figures are: closed valvotomy—fetal mortality 5–15%, maternal 3%, open valvotomy—fetal mortality 15–33%, maternal 5%.
- Women with MS should avoid the supine and lithotomy positions as much as possible for labour and delivery. Fluid overload must be avoided, and even in the presence of oliguria, without significant blood loss, the temptation to give intravenous fluids must be resisted. Pulmonary oedema, if it occurs, should be treated in the usual way with oxygen and diuretics, and introduction or reintroduction of a β -blocker may be useful to slow the heart rate.

1 Desai DK, Adanlawo M, Naidoo DP, et al. (2000). Mitral stenosis in pregnancy: a four-year experience at King Edward VIII Hospital. *Br J Obstet Gynaecol* **107**: 953–8.

2 Tsiaras S, Poppas A (2009) Mitral valve disease in pregnancy: outcomes and management. *Obstet Med* **2**: 6–10.

Other valve lesions

Mitral regurgitation

Usually due to MV prolapse. Well tolerated as systemic vascular resistance is low in pregnancy. LV function is important in assessing risk (normal function carries a good prognosis).

Aortic stenosis

Usually congenital. If severe/symptomatic, advise deferring pregnancy until surgically corrected. If already pregnant and symptomatic early on, consider termination. Surgical replacement/balloon valvuloplasty are both associated with significant risks.

Aortic regurgitation

Usually well tolerated as reduced systemic vascular resistance in pregnancy reduces the regurgitant volume. Vasodilators/diuretics are usually sufficient treatment (stop angiotensin-converting enzyme inhibitor (ACE-I) and replace with nifedipine, hydralazine, etc.).

Mechanical heart valves in pregnancy

The optimal management of women with metal heart valve replacements in pregnancy is controversial, since the interests of the mother and the fetus are in conflict. These women require lifelong anticoagulation and this must be continued in pregnancy because of the increased risk of thrombosis. Warfarin is associated with warfarin embryopathy if given between 6 and 12 weeks' gestation,¹ and increased risks of miscarriage, stillbirth, and fetal intracerebral haemorrhage.² There is some evidence that the adverse effects of warfarin are related to the dose required to maintain the international normalized ratio (INR) >2 , with doses in excess of 5 mg being associated with higher risks of teratogenesis, miscarriage and, stillbirth.³ Heparin and low molecular weight heparin, even in full anticoagulant doses, are associated with increased risks of valve thrombosis and embolic events.¹⁻⁴

Management

There are three basic options:

- continue warfarin throughout pregnancy, stopping only for delivery; this is the safest option for the mother^{1,2}
- replace the warfarin with high-dose unfractionated or low-molecular weight heparin from 6 to 12 weeks' gestation to avoid warfarin embryopathy
- use high-dose unfractionated or low-molecular weight heparin throughout pregnancy.⁴

Which option is chosen will depend on several factors:

- the type of mechanical valve—the risk of thrombosis is less with the newer bileaflet valves (e.g. CarboMedics) than with the first-generation ball and cage (e.g. Starr–Edwards), or second-generation single tilting disc (e.g. Bjork–Shiley) valves
- the position of the valve replacement—valves in the aortic rather than the mitral position, are associated with a lower risk of thrombosis⁵
- the number of mechanical valves
- the dose of warfarin required to maintain a therapeutic INR³
- any previous history of embolic events.

Whichever management option is chosen, warfarin should be discontinued and substituted for heparin for 10 days prior to delivery, to allow clearance of warfarin from the fetal circulation. For delivery itself, heparin therapy is interrupted. Warfarin is recommenced 3–5 days post-partum. In the event of bleeding, or the need for urgent delivery in a fully anticoagulated patient, warfarin may be reversed with fresh frozen plasma (FFP)

1 Chan WS, Anand S, Ginsberg JS (2000). Anticoagulation of pregnant women with mechanical heart valves. *Arch Intern Med* **160**: 191–6.

2 Sadler L, McCowan L, White H, et al. (2000). Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *Br J Obs Gynaecol* **107**: 245–53.

3 Cotrufo M, De Feo M, De Santo L, et al. (2002). Risk of warfarin during pregnancy with mechanical valve prostheses. *Obstet Gynecol* **99**: 35–40.

4 Oran B, Lee-Parritz A, Ansell J (2004). Low molecular weight heparin for the prophylaxis of thromboembolism in women with prosthetic mechanical heart valves during pregnancy. *Thromb Haemost* **92**: 747–51.

5 Elkayam U (1999). Pregnancy through a prosthetic heart valve. *J Am Coll Cardiol* **33**: 1642–5.

and vitamin K, and heparin with protamine sulphate. Vitamin K should be avoided if possible, since it renders the woman extremely difficult to anticoagulate with warfarin after delivery.

Anticoagulation in pregnancy

- *Low molecular weight heparin (LMWH)*: Effective anticoagulant. Does not cross placenta. Good bioavailability following subcutaneous administration. Easy weight-based dosing schedule. Thrombocytopenia and osteoporosis are extremely rare. *Side-effects*: maternal haemorrhage, wound haematoma, local allergic reaction at injection site.
- *Unfractionated heparin*: Rarely used since LMWHs have become the anticoagulants of choice in pregnancy. Use in pregnancy is mainly intravenous and confined to acute management of massive pulmonary emboli and in the peri-partum period it is used for rapid control (and reversal) of anticoagulation in case emergency delivery is required. Not effective for use with mechanical valves in pregnancy. *Side-effects*: maternal haemorrhage, thrombocytopenia (monitor full blood count (FBC)), osteoporosis, alopecia.
- *Warfarin*: Effective oral anticoagulant. Crosses the placenta. Increases risk of miscarriage and stillbirth. Studies show it to be more effective than unfractionated heparin at preventing valve thrombosis in pregnancy. *Side-effects*: fetal and maternal haemorrhage, teratogenic in first trimester therefore avoid during this period if at all possible (use LMWH).
- *Aspirin*: Used in low dose (75 mg) as adjunctive therapy with LMWH for pregnant women with prosthetic valves and also in other high-risk patients (atrial fibrillation (AF), LV dysfunction, previous emboli).

Ischaemic heart disease

The risk factors for change to acute coronary syndrome (ACS) MI in pregnancy are the same as for the non-pregnant individual. The risk is increased in multigravid women and in those who smoke, and women with diabetes, obesity, hypertension, and hypercholesterolaemia.¹ Infarction most commonly occurs in the third trimester and affects the anterior wall of the heart.¹ The maternal death rate is about 10%. In pregnancy, aetiologies other than atherosclerosis are more likely (such as coronary artery thrombosis or dissection) than in the non-pregnant woman.²

Management

- Management of ACS is as for the non-pregnant woman.
- Angiography should not be withheld if clinically indicated.
- Intravenous and intracoronary thrombolysis and percutaneous transluminal coronary angioplasty and stenting have all been successfully performed in pregnancy.
- Both aspirin and β -blockers are safe in pregnancy.
- Clopidogrel also seems to be safe, although it should be discontinued prior to delivery because of the increased bleeding risk.
- Glycoprotein IIb/IIIa inhibitors should be avoided although there are case reports of their successful use.
- Statins should be discontinued prior to pregnancy as they are associated with an increased risk of malformations.

1 Ladner, HE, Danielsen B, Gilbert WM (2005). Acute myocardial infarction in pregnancy and the puerperium: a population-based study. *Obstet Gynecol* **105**: 480–4.

2 Roth A, Elkayam U (1996). Acute myocardial infarction associated with pregnancy. *Ann Intern Med* **125**: 751–7.

Hypertrophic cardiomyopathy

The danger of hypertrophic cardiomyopathy (HCM) in pregnancy relates to LVOT obstruction that may be precipitated by hypotension or hypovolaemia. Provided these are avoided, pregnancy is usually well tolerated.

Management

- β -blockers should be continued in pregnancy or initiated for symptomatic women.
- Epidural anaesthesia/analgesia carries the risk of vasodilatation and hypotension, with consequent increased LVOT obstruction. Any hypovolaemia will have the same effect and should be rapidly and adequately corrected.

Peripartum cardiomyopathy

This pregnancy-specific condition is defined as the development of cardiac failure between the last month of pregnancy and 5 months post-partum, in the absence of an identifiable cause or recognizable heart disease prior to the last month of pregnancy, and LV systolic dysfunction. The diagnosis should be suspected in the puerperal patient with breathlessness, tachycardia, or signs of heart failure. It is confirmed with echocardiography.

Echocardiographic criteria for peripartum

LV dysfunction:¹

- LVEF < 45%
- Fractional shortening < 30%
- LVEDP (left ventricular end-diastolic pressure) > 2.7 cm/m²
- Often, echocardiography shows the heart is enlarged with global dilatation of all four chambers and markedly reduced LV function.

Risk factors include:

- multiple pregnancy
- hypertension (be it pre-existing or related to pregnancy or pre-eclampsia)
- multiparity
- increased age
- African-Caribbean race.

Management

Treatment is as for other causes of heart failure, with:

- oxygen
- diuretics
- vasodilators
- cardioselective β -blockers
- ACE-Is if post-partum
- inotropes if required
- LV assist devices
- heart transplantation.

About 50% of women make a spontaneous and full recovery. Most case fatalities occur close to presentation. Recent data show a 5-year survival of 94%.² Prognosis and recurrence depend on the normalization of LV size within 6 months of delivery.³ Those women with severe myocardial dysfunction, defined as LV end-diastolic dimension ≥ 6 cm and fractional shortening $\leq 21\%$, are unlikely to regain normal cardiac function on follow-up.⁴ Those whose LV function and size do not return to normal within 6 months and prior to a subsequent pregnancy are at significant risk of

1 Pearson GD, Veille JC, Rahimtoola S, et al. (2000). Peripartum Cardiomyopathy. National Heart, Lung and Blood Institute and Office of Rare Diseases (NIH). Workshop Recommendations and Review. *JAMA* **283**: 1183–88.

2 Felker GM, Thompson RE, Hare JM, et al. (2000). Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* **342**: 1077–84.

3 Elkayam U, Tummala PP, Rao K, et al. (2001). Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med* **344**: 1567–71.

4 Witlin AG, Mabie WC, Sibai BM (1997). Peripartum cardiomyopathy: a longitudinal echocardiographic study. *Am J Obstet Gynecol* **177**: 1129–32.

worsening heart failure (50%) and death (25%) or recurrent peripartum cardiomyopathy in the next pregnancy. They should therefore be advised against pregnancy.⁵ Those who do recover normal LV size and function may still be at risk of recurrent heart failure in a subsequent pregnancy, either because of a new episode of cardiomyopathy or because they have impaired contractile reserve. To exclude the latter, a stress ECHO is advisable prior to any future pregnancy.⁶

5 Sliwa K, Fett J, Elkayam U (2006) Peripartum cardiomyopathy. *Lancet* **368**: 687–93.

6 Nelson-Piercy C (2006) Cardiomyopathy and pregnancy. In Steer P, Gatzoulis M, Baker P (eds). *Cardiac Disease in Pregnancy*. London: RCOG Press, pp. 231–42.

Arrhythmias in pregnancy

Atrial and ventricular premature complexes (APC, VPC) are common in pregnancy. Many pregnant women are symptomatic from forceful heart beats that occur following a compensatory pause after a VPC. Most women with symptomatic episodes of dizziness, syncope, and palpitations do not have arrhythmias.¹

A sinus tachycardia requires investigation for possible underlying pathology such as:

- blood loss
- infection
- heart failure
- thyrotoxicosis
- pulmonary embolus.

The commonest arrhythmia encountered in pregnancy is supraventricular tachycardia (SVT). First onset of SVT (both accessory pathway-mediated and AV nodal re-entrant) is rare in pregnancy, but 22% of 63 women with SVT had exacerbation of symptoms in pregnancy;² 50% of SVTs do not respond to vagal manoeuvres.

Management

- Propranolol, verapamil, and adenosine have Food and Drug Administration (FDA) approval for acute termination of SVT. Adenosine has advantages over verapamil, including probable lack of placental transfer, and may be safely used in pregnancy for SVTs that do not respond to vagal stimulation.^{3,4}
- Metoprolol is short acting and may be used to prevent or reduce symptomatic SVTs in pregnancy. Flecainide is safe and is also used in the treatment of fetal tachycardias.
- Propafenone and amiodarone should be avoided,⁵ the latter because of interference with fetal thyroid function.
- Temporary and permanent pacing, cardioversion, and implantable defibrillators are also safe in pregnancy.^{3,4}

1 Lee SH, Chen SA, Wu TJ, et al. (1995). Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. *Am J Cardiol* **76**: 675–8.

2 Page RL (1995). Treatment of arrhythmias during pregnancy *Am Heart* **130**: 871–6.

3 Mason BA, Ricci-Goodman J, Koos BJ (1992). Adenosine in the treatment of maternal paroxysmal supraventricular tachycardia. *Obstet Gynecol* **80**: 478–80.

4 Adamson D, Nelson-Piercy C (2007). Palpitations and arrhythmias in pregnancy. *Heart* **93**: 1630–6.

5 Magee LA, Downar E, Sermer M, et al. (1995). Pregnancy outcome after gestational exposure to amiodarone. *Am J Obstet Gynecol* **172**: 1307–11.

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Cardiac arrest in pregnancy

This should be managed according to the same protocols as used in the non-pregnant woman, with two very important additions:

- pregnant women (especially those in advanced pregnancy) should be 'wedged' to relieve any obstruction to venous return from pressure of the gravid uterus on the IVC. This can be most rapidly achieved by turning the patient into the left lateral position. If cardiopulmonary resuscitation (CPR) is required, then the pelvis can be tilted while keeping the torso flat to allow external chest compressions.
- The most senior member of the obstetric team should be summoned. This is to ensure that obstetric causes of the collapse are considered (e.g. amniotic fluid embolism, massive post-partum haemorrhage) and appropriately treated. In addition, emergency caesarean section may be required to aid maternal resuscitation.

Endocarditis prophylaxis

- Current UK recommendations from the National Institute for Health and Clinical Excellence (NICE) 2008 are that antibiotic prophylaxis against infective endocarditis (IE) is not required for childbirth.
- The British Society for Antimicrobial Chemotherapy (BSAC) 2006, and the American Heart Association (AHA) have recommended cover only for patients deemed to be at high risk of developing IE (such as women with previous IE) and for those who have the poorest outcome if they develop IE (such as those with cyanotic congenital heart disease).
- Fatal cases of endocarditis in pregnancy have occurred antenatally, rather than as a consequence of infection acquired at the time of delivery. If antibiotic prophylaxis is used for delivery it should be:
 - amoxicillin 2 g IV plus gentamicin 1.5 mg/kg IV at the onset of labour or ruptured membranes, or prior to caesarean section, followed by amoxicillin 500 mg orally (or IM/IV depending on the patient's condition) 6 hours later
 - for women who are allergic to penicillin, vancomycin 1 g IV or teicoplanin 400 mg IV may be used instead of amoxicillin.

Eponymous syndromes

Syndromes are listed in alphabetical order *698–708*

A–C

Aase syndrome A clinical triad of congenital anaemia, triphalangeal thumbs, and VSD. The aetiology is unknown.

Adams–Stokes syncope See Stokes–Adams syndrome (📖 p. 706).

Alfidi's syndrome Hypertension resulting from occlusion of the coeliac axis, leading to diversion of collateral blood flow from the right renal artery. Originally described as renal-splanchnic steal syndrome.¹

Andersen syndrome A triad of periodic paralysis, ventricular tachyarrhythmias, and dysmorphic features (hypertelorism, micrognathia, low-set ears, and high arched or cleft palate, short stature, scoliosis, syndactyly, and clinodactyly). The periodic paralysis can be associated with hyper-, hypo-, or normokalaemia. It is an autosomal dominant condition associated with mutations in the *KCNJ2* gene encoding the inward-rectifying K⁺ channel Kir2.1.²

Anderson–Fabry disease A rare X-linked recessive lysosomal storage disorder involving a deficiency of the enzyme alpha galactosidase. There is a resulting accumulation of globotriaosylceramide throughout the body. Cardiac manifestations include left and right ventricular hypertrophy and heart failure. Other systemic features include renal impairment, angiokeratomas, neuropathy, and corneal keratopathy. Treatment is now available in the form of enzyme-replacement therapy.

Barlow's syndrome A familial form of mitral valve prolapse which is sometimes inherited as an autosomal dominant trait. It is a genetically heterogeneous syndrome, characterized by 'billowing' of one or both of the mitral valve leaflets into the left atrium during systole. On auscultation there is a midsystolic click and a late or pansystolic murmur. 20% are asymptomatic. Females are twice as commonly affected.³

Barth syndrome An X-linked mutation of the *TAZ* gene, leading to dilated cardiomyopathy, skeletal myopathy, short stature and neutropenia. 3-methylglutaconic acid excretion in the urine has been observed in almost all reported cases.

Beemer lethal malformation syndrome A lethal syndrome of double outlet right ventricle, hydrocephalus, dense bones, thrombocytopenia, and abnormal nasal development.

1 Alfidi RJ, Filson EJ, Frohlich ED, Gifford RW Jr, Meaney TF (1967). Renal-splanchnic steal. Report of a case. *Cleveland Clin Q* **34**: 43–54.

2 Donaldson MR, Jensen JL, Tristani-Firouzi M, et al. (2003). PIP2 binding residues of Kir2.1 are common targets of mutations causing Andersen syndrome. *Neurology* **60**(11): 1811–16.

3 Barlow J, Marchand BP, Pocock WA, Denny D (1963). The significance of late systolic murmurs. *Am Heart J* **66**: 443.

Bland–Garland–White syndrome (or ALCAPA) A congenital condition featuring anomalous origin of the left coronary artery arising from the pulmonary artery (ALCAPA) resulting in myocardial ischaemia. Affected infants typically present with congestive heart failure within the first 1–2 months of life. Definitive treatment involves surgical re-implantation of the left coronary artery or bypass grafting.¹

Bouillaud's syndrome An eponym for rheumatic fever. Bouillaud was the first to emphasize the importance of cardiac involvement in the acute articular phase of rheumatic fever.²

Bourneville–Pringle disease Hamartomas of the heart and kidney associated with epilepsy, learning difficulties, cerebral cortical hamartomas (tuberosc sclerosis), and adenoma sebaceum. It is inherited in an autosomal dominant manner. Renal cysts or carcinomas may occur.³

Bradbury–Eggseton syndrome An idiopathic disorder of autonomic failure characterized by orthostatic hypotension, with more widespread manifestations of thermoregulatory, bowel, bladder, and sexual function disturbance.

Brugada's syndrome One of the principal causes of sudden cardiac death in young adults in the absence of structural heart disease, secondary to mutation of the *SCN5A* gene on chromosome 3, inherited in an autosomal dominant fashion. This results in malfunction of a sodium channel leading to initiation and perpetuation of ventricular arrhythmias. Clinically there is right bundle branch block, ST elevation in V₁ to V₃, and sudden death/syncope. The clinical phenotype may be unmasked by the administration of ajmaline (not available in the UK) or procainamide. The only effective treatment is with an implantable cardiac defibrillator.⁴

Carney syndrome Also known as the Carney complex. There is association of atrial myxomas with myxomas in other locations, e.g. breast or skin, spotty pigmentation, and endocrine overactivity, e.g. pituitary or testicular tumours. The inheritance is autosomal dominant, the mutation being in the *PRKAR1A* gene on chromosome 17. It tends to affect individuals in their third decade. They are more likely to have bilateral myxomas and develop recurrences of the myxoma after removal, in contrast to sporadic cases.

1 Bland EF (1933). Congenital anomalies of the coronary arteries: report of an unusual case associated with cardiac hypertrophy. *Am Heart J* 8: 787–801.

2 Bouillaud B (1832). *Traité clinique du rhumatisme articulaire*. Paris.

3 Bourneville DM (1880). Sclérose tubéreuse des circonvolution cérébrales: Idiotie et épilepsie hémiplégique. *Archives de neurologie Paris* 1: 81–91.

4 Brugada P, Brugada J (1992). Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 20(6): 1391–6.

D–M

DiGeorge syndrome A disorder resulting from deletion of the *TBX1* gene on chromosome 22q11.2, leading to parathyroid hypoplasia (and hypocalcaemia), thymic hypoplasia (and low T-cell counts), and outflow tract defects of the heart, including tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, right-sided aortic arch, and aberrant right subclavian artery. Affected individuals typically have micrognathia, low-set ears, short philtrum, and small mouth. The Shprintzen syndrome is also caused by a disorder in the same gene.

Dressler syndrome A myocardial infarction-associated pericarditis, usually occurring one week after the onset of infarction, but may occur several months afterwards. An autoimmune aetiology is suspected due to the delay in development of the syndrome, the presence of antibodies against the heart, evidence of altered lymphocyte subsets and complement activation, frequent recurrences, associated pleuritis and pleural effusions, and response to non-steroidal drugs and steroids. There may be a pericardial rub, fever, pericardial and pleural effusions, with PR abnormalities, as well as ST- and T-wave changes suggestive of pericarditis.

Duchenne muscular dystrophy An X-linked disorder of the dystrophin gene. There is severe skeletal muscle weakness, which may mask dilated cardiomyopathy. There is a tendency for fibrosis to affect the posterolateral and posterobasal left ventricular wall. Supraventricular arrhythmias are more common than ventricular arrhythmias and heart block, which occur as the fibrosis becomes more widespread.

Ebstein's anomaly A malformation in which there is an abnormal attachment of the tricuspid valve leaflets leading to a downward displacement of the tricuspid valve. A portion of the right ventricle therefore lies between the atrioventricular (AV) ring and the origin of the valve, so that the proximal part of the right ventricle is 'atrialized', and a small right ventricular chamber exists. Tricuspid valve tissue is dysplastic. There is spectrum of severity in this condition, and it is associated with pulmonary stenosis or atresia, as well as VSD and ostium primum atrial septal defect (ASD).

Eisenmenger syndrome Any systemic-to-pulmonary circulation shunt that eventually leads to reversal or bidirectional flow of the shunt, with subsequent pulmonary hypertension and cyanosis. It was first described in a 32-year-old man with a ventricular septal defect in 1897.¹

Ellis–Van Creveld syndrome An autosomal recessive condition characterized by short stature caused by metaphyseal dysplasia, polydactyly, dysplastic nails and teeth, and, most commonly, primum ASD. Coarctation of the aorta, hypoplastic left heart, and patent ductus arteriosus (PDA) occur in 20% of cases.

¹ Eisenmenger, V (1897). Die angeborenen Defekte der Kammerscheidewände des Herzens. *Zeitschrift für klinische Medizin* **32**(suppl): 1–28.

Emery–Dreifuss muscular dystrophy A clinical triad of early contractures of the elbow, Achilles tendon, and posterior cervical muscles, progressive skeletal myopathy, and cardiac manifestations. These include sinus bradycardia, atrial fibrillation and atrial flutter initially, progressing to higher levels of AV block, sustained ventricular tachycardia and ventricular fibrillation. Heart failure may also be present. Sudden death before the age of 50 years is common. It is X-linked in its transmission, with the gene responsible encoding a nuclear membrane protein called emerin.¹

Fabry disease See Anderson–Fabry disease (📖 p.438, p.698).

Fallot's tetralogy The association of pulmonary stenosis, ventricular septal defect, over-riding aorta, and right ventricular hypertrophy, causing cyanosis in the newborn. This forms 10% of all congenital heart disease, and is slightly more common in males. Fallot's trilogly comprises pulmonary stenosis, strial septal defect, and intact ventricular septum, Fallot's pentalogy is the addition of an atrial septum defect or patent foramen ovale to the tetralogy.²

Friedreich's ataxia A spinocerebellar degenerative disease characterized by limb and trunk ataxia, skeletal deformities, dysarthria, and cardiomyopathy. Concentric left ventricular hypertrophy frequently occurs, as well as asymmetrical septal hypertrophy. Rarer is dilated cardiomyopathy. There may be associated atrial arrhythmias. The condition is inherited in an autosomal dominant manner, with the mutation identified as an amplified, unstable GAA trinucleotide repeat found in the first intron of the frataxin gene on chromosome 9q13.

Friedreich's disease Sudden collapse of the cervical veins that were previously distended at each diastole, caused by an adherent pericardium. Also known as mediastinopericarditis adhesiva, or Friedreich's sign.

Holt–Oram syndrome An autosomal dominant condition, sometimes known as heart–hand syndrome, in which there is dysplasia of the upper limbs associated most commonly with secundum ASD, but also with VSD, mitral valve prolapse, and PDA. The arm deformities may be subtle, from having distally placed or triphalangeal thumbs, to more severe forms including hypoplastic clavicles and phocomelia.

¹ Muntoni F (2003). Cardiomyopathy in muscular dystrophies. *Curr Opin Neurol* **16**(5): 577–83.

² Fallot ELA (1888). *Contribution à l'Anatomie Pathologique de la Maladie Bleue (Cyanose Cardiaque)*. Marseille: Marseille Médical.

Heyde's syndrome The association of gastrointestinal bleeding and calcific aortic stenosis. Since Heyde's original description in 1958, the bleeding has been shown to be due to an acquired von Willebrands disease type 2a caused by high shear stress around the aortic valve, leading to haemorrhage from arteriovenous malformations in the gut. The bleeding abnormality ceases after replacement of the valve.^{1,2}

Hurler's syndrome An autosomal recessive mucopolysaccharide storage disorder resulting from deficiency of the lysosomal enzyme alpha-L-iduronate. It is also designated mucopolysaccharidosis type IH (MPSIH). Clinical features include coarse facial characteristics, corneal clouding, hepatosplenomegaly, thickened skin, mental retardation, and cardiac problems. These consist of restrictive cardiomyopathy due to endomyocardial fibroelastosis, coronary artery stenosis, and valvular thickening (left side more than right side) and regurgitation. Most die in the first decade. Hunter's syndrome is MPS II, and pursues a slower course. Scheie syndrome is MPS IS, and has the most benign course of the mucopolysaccharidoses.³

Jervell-Lange-Nielsen syndrome An autosomal recessive condition associated with deafness caused by mutation in the *KVLQT1* gene, or the *KCNE1* gene, both encoding components of the delayed rectifier potassium channel involved in the action potential. As a result, the QT interval is prolonged and affected individuals have a variable risk of developing torsade de pointes and sudden cardiac death (SCD).

Kartagener's syndrome A clinical triad of situs inversus, abnormal frontal sinuses, and immotile cilia. The patient has recurrent respiratory infections, sinusitis, bronchiectasis, and infertility. Some may have anosmia, or low levels of immunoglobulin A (IgA). Inheritance is autosomal recessive. The defect lies in the genes encoding the dynein protein that contributes to the structure of cilia. Also known as the Siewert syndrome.⁴

Kawasaki disease An acute vasculitis that affects children, which manifests with fever, cervical lymphadenopathy, bilateral conjunctivitis, erythema or desquamation of the palms and soles, and coronary artery aneurysms or ectasia. These may lead to myocardial infarction and sudden death. The aetiology is unknown.⁵

1 Heyde EC (1958). Gastrointestinal bleeding in aortic stenosis. *N Engl J Med* **259**: 196.

2 Batur P (2000). Increased prevalence of aortic stenosis in patients with arteriovenous malformations of the gastrointestinal tract in Heyde Syndrome. *Arch Intern Med* **163**: 1821–4.

3 Hurler G (1919). *Über einen Typ multipler Abartungen, vorwiegend am Skelettsystem*. Zeitschrift für Kinderheilkunde, Berlin **24**: 220–234.

4 Kartagener M (1933). Zur Pathogenese der Bronchiektasien: Bronchiektasien bei Situs viscerum inversus. *Beiträge zum Klinik der Tuberkulose* **83**: 489–501.

5 Kawasaki T (1967). Acute febrile mucocutaneous syndrome with mucoid involvement with specific desquamation of the fingers and toes in children. *Jpn J Allergy* **116**: 178.

Kearns–Sayre syndrome A clinical triad of AV block, pigmentary retinopathy, and progressive external ophthalmoplegia. It is caused by the deletion of several mitochondrial genes. In most cases it occurs sporadically and is not inheritable.¹

Leber hereditary optic neuropathy A mitochondrial encephalomyopathy characterized by painless loss of vision in a young man. There may be an associated short PR interval and pre-excitation.²

Lenegre–Lev disease Also known as progressive familial heart block type I (PFHBI). An autosomal dominant disorder mapped to chromosome 19, defined by evidence of bundle branch block with wide QRS complexes that may progress to complete heart block. This is distinct from progressive familial heart block type II (PFHBII), which has narrow QRS complexes. There is an accelerated degenerative process that primarily affects the conduction tissue.

Löffler's syndrome A rare form of endocarditis associated with high levels of circulating eosinophils. The underlying cause may be helminthic infection or leukaemia, but in most it is unknown. Typically, the lungs are involved with diffuse reticular nodular shadowing on the chest X-ray. The acute form is characterized by an eosinophilic vasculitis that leads to dilated cardiac chambers, whereas the chronic form leads to fibrosis of myocardium leading to a clinical syndrome of restrictive cardiomyopathy, resulting in reduced effort tolerance, wheezing, hepatomegaly, heart block, mitral and tricuspid regurgitation, and systemic embolization.

Lown–Ganong–Levine syndrome A ventricular pre-excitation phenomenon characterized by a short PR interval (<120 ms) and normal QRS duration, in association with paroxysms of supraventricular tachycardia but not atrial flutter or fibrillation. Patients without a history of tachycardia may be described as having accelerated AV nodal conduction. Although first described by Clerc in 1938, the eponymous individuals reported this syndrome in 1952. No single structural abnormality has been found to be the cause of this syndrome. It may be due to intranodal or paranodal fibres that bypass the AV node. Most patients at electrophysiological study have been found to have a reason other than a bypass tract for their paroxysmal tachycardia, such as atrioventricular node re-entrant tachycardia (AVNRT). Therefore, this is a syndrome of a pre-electrophysiological study era that describes a clinical phenomenon of paroxysmal tachycardia with a short PR interval that may be at one end of the normal range (2–4% of adults have PR<120 ms).³

1 Schmitz K, Lins H, Behrens-Baumann W (2003). Bilateral spontaneous corneal perforation associated with complete external ophthalmoplegia in mitochondrial myopathy (Kearns–Sayre syndrome). *Cornea* **22**(3): 267–270.

2 Leber (1868). Beiträge zur Kenntniss der atrophischen Veränderungen des Sehnerven nebst Bemerkungen über normale Structur des Nerven. *Archiv für Ophthalmologie, Berlin* **14**: 164–76.

3 Lown B, Ganong WF, Levine SA (1952). The syndrome of short PR interval, normal QRS complex, and paroxysmal rapid heart action. *Circulation* **5**: 693–706.

Libman–Sacks syndrome A cardiac manifestation of systemic lupus erythematosus, which occurs late in the disease process, and is found in 50% of patients with fatal lupus at post-mortem. It is characterized by sterile, verrucous lesions on valve leaflets and chordae consisting of fibrin, neutrophils, lymphocytes, and histiocytes. The mitral and aortic valves are most commonly affected, although most cases are clinically silent. Valvular regurgitation is more common than stenosis. Similar lesions may occur in association with the antiphospholipid syndrome. Women are more commonly affected.¹

Lutembacher's syndrome The combination of mitral stenosis (congenital or acquired) and ASD (congenital or iatrogenic), with left-to-right shunt. If the ASD is large, pulmonary hypertension is avoided, but with the consequence of progressive right heart dilatation.²

Marfan syndrome A disorder resulting from mutations in the *FBN1* gene on chromosome 15q21.1 encoding fibrillin-1, which constitutes the microfibrils that make up the extracellular matrix. Features include tall stature, kyphosis, scoliosis, pectus excavatum, upwards lens dislocation, dural ectasia, retinal detachment, and a variety of cardiac abnormalities. These include mitral valve prolapse and regurgitation, dilated sinuses of Valsalva, aortic root dilatation with aortic regurgitation and increased risk of dissection, and arrhythmias. Patients may be at increased risk of endocarditis secondary to the valve abnormalities. 75% are inherited as autosomal dominant; the remainder occur sporadically.³

Morquio's syndrome One of the mucopolysaccharide storage disorders, designated mucopolysaccharidosis IVB (MPSIVB), inherited in an autosomal recessive manner. Two types are recognized. Type A is caused by deficiency of galactosamine-6-sulphatase, whereas type B is caused by deficiency in beta galactosidase. Clinical features include short stature, skeletal and joint abnormalities, cloudy corneas, hepatomegaly, and aortic and mitral regurgitation. Heart failure may result from either an infiltrative cardiomyopathy or valvular regurgitation.⁴

1 Libman E, Sacks B (1924). A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med Chicago* **33**: 701–37.

2 Lutembacher R (1916). De la sténose mitrale avec communication interauriculaire. *Archives des Maladies du Cœur et des Vaisseaux Paris* **9**: 237–60.

3 Marfan AB (1896). Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'aminicissement. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris* **13**: 220–6.

4 Morquio L (1929). Sur une forme de dystrophie osseuse familiale. *Archives de Médecine des Enfants, Paris* **32**: 129–35.

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N–W

Noonan's syndrome A dysmorphic syndrome characterized by cardiac anomalies, short stature, low-set ears, hypertelorism, deafness, and bleeding diathesis. It is inherited in an autosomal dominant manner. Cardiac problems include valvular pulmonary stenosis. This syndrome has sometimes been called 'male Turner's syndrome', although it affects both sexes, and, in contrast, has no chromosomal abnormalities.¹

Ortner's syndrome First described as compression of the recurrent laryngeal nerve by a dilated left atrium in mitral valve stenosis, giving rise to a hoarse voice from vocal cord paresis. Sometimes used to describe any non-malignant cardiac or intrathoracic process that damages the recurrent laryngeal nerve. The left nerve is more commonly affected than the right, due to its longer course around the aortic arch.

Pompe disease An autosomal recessive metabolic disorder caused by an accumulation of glycogen within lysosomes due to deficiency of the enzyme alpha-glucosidase. Cardiac manifestations include left ventricular hypertrophy, outflow tract obstruction, and heart failure. The disease can present in infants, juveniles, or adults. Treatment is available in the form of enzyme-replacement therapy.²

Prinzmetal's (variant) angina Angina resulting from spasm of a coronary artery, which may lead to heart block and myocardial infarction. It may be prevented by long-acting calcium antagonists.³

Romano–Ward syndrome An autosomal dominant condition caused by mutation in genes on chromosomes 3, 4, 7, 11, and 21 encoding different components of both sodium and potassium channels. The QT interval is prolonged and there is a high risk of developing torsades de pointes and sudden cardiac death (SCD). It is not associated with deafness and is therefore distinct from Jervell–Lange–Nielsen syndrome.

Shprintzen syndrome A disorder caused by mutation in the *TBX1* gene, which is also responsible for the DiGeorge syndrome. The characteristic features are cardiac anomalies (most commonly VSD), cleft palate, learning difficulties, and typical facies including prominent nose, narrow palpebral fissures, and micrognathia. Also known as the velocardiofacial syndrome.

Stokes–Adams syndrome Syncope caused by cardiac arrhythmia. Also known as Spens syndrome and Morgagni's syndrome.^{4,5}

1 Noonan A, Ehmke DA (1963). Associated noncardiac malformations in children with congenital heart disease. *J Pediatr St Louis* **63**: 468–70.

2 Pompe JC (1932). Over idiopathische hypertrophie van het hart. *Ned Tijdschr Geneeskde* **76**: 304–12.

3 Prinzmetal M, Massumi RA (1955). The anterior chest wall syndrome—chest pain resembling pain of cardiac origin. *JAMA* **159**: 177–84.

4 Adams R (1827). Cases of diseases of the heart, accompanied with pathological observations. *Dublin Hospital Reports* **4**: 353–453.

5 Stokes W (1846). Observations on some cases of permanently slow pulse. *Dublin Q J Med Sci* **2**: 73–85.

Sydenham's chorea A delayed manifestation of rheumatic fever, due to an inflammatory reaction caused by autoantibodies in the basal ganglia and caudate nuclei, following group A streptococcal infection. It usually occurs three months after the initial infection and symptoms may last for up to two weeks. It is characterized by involuntary movements, muscle incoordination, and emotional lability.

Takotsubo cardiomyopathy A syndrome that mimics acute coronary syndrome, with chest pain, ischaemic electrocardiogram (ECG) changes, and elevated cardiac enzymes. It is typically triggered by emotional or physical stress. Angiography usually demonstrates unobstructed coronary arteries, and characteristic echocardiography findings include ballooning of the left ventricular apex with a hypercontractile base, which earned the syndrome its name, meaning 'octopus trap' in Japanese. Treatment is supportive and patients usually recover completely.¹

Taussig-Bing syndrome A congenital anomaly in which the aorta arises from the right ventricle, the pulmonary artery arises from both ventricles, and there is an associated VSD.²

Tietze's syndrome Inflammation of the costochondral cartilages of unknown aetiology. There is characteristic swelling of the cartilages, which distinguishes the syndrome from other types of costochondritis, and the swelling may persist after the pain has resolved. Mostly men in their third decade are affected.³

Townes-Brocks syndrome An autosomal dominant condition describing the association of imperforate anus, and abnormalities of the kidneys, hand, foot, and ear, sporadically associated with cardiac malformations including VSD and ASD.

Turner's syndrome A disorder resulting from the absence of one of the X chromosomes, XO. Features include coarctation of the aorta, short stature, absence of secondary sexual characteristics, webbing of the neck, cubitus valgus, and lymphoedema. It is one of the most common chromosomal abnormalities.⁴

1 Sato H, Tateishi H, Uchida T, Dote K, Ishihara M, Sasaki K et al (1990). Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, eds. *Clinical Aspect of Myocardial Injury: from ischaemia to heart failure*. Tokyo: Kagakuhyouronsya: pp. 56–64.

2 Taussig HB, Bing RJ (1949). Complete transposition of the aorta and levoposition of the pulmonary artery: clinical, physiological, and pathological findings. *Am Heart J, St Louis* 37: 551–9.

3 Tietze A (1921). Über eine eigenartige Häufung von Fällen mit Dystrophie der Rippenknorpel. *Berliner klinische Wochenschrift* 58: 829–31.

4 Turner HH (1938). A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology* 23: 566–74.

Twiddler's syndrome Not strictly an eponym. The phenomenon of permanent malfunction of a pacemaker due to the patient's manipulation of the pulse generator.¹

Wenkebach's heart A description of a heart located in the midline which is smaller than normal. Also known as mesocardia, or the 'hanging heart'.

Wenkebach's phenomenon A form of second degree atrioventricular heart block characterized by progressive lengthening of the PR interval on the ECG until a P wave is not conducted to the ventricles.²

Williams syndrome A congenital supravalvular aortic stenosis associated with peripheral pulmonary artery stenosis, hypercalcaemia, elfin facies, outgoing personality, learning difficulties, strabismus, and dental anomalies. The left ventricle may be hypertrophied, and the sinuses of Valsalva may be dilated. In addition, the coronary arteries may be dilated or tortuous, and demonstrate accelerated atherosclerosis. The patient is at higher risk of endocarditis and sudden death than unaffected individuals. Autosomal dominant transmission is observed if this syndrome is inherited.

Wolff-Parkinson-White syndrome Tachyarrhythmias that occur as a result of an accessory atrioventricular pathway, typified by the ECG features in sinus rhythm of a PR interval less than 120 ms and QRS duration greater than 120 ms caused by a delta wave, representing antegrade conduction through the accessory pathway. Patients can have intermittent conduction via this pathway, leading to variable ECG patterns.³

1 Bayliss CE, Turner HH (1968). The pacemaker-twiddler's syndrome: a new complication of implantable transvenous pacemakers. *Can Med Assoc J* **99**(8): 371–3.

2 Wenkeback KF (1898). De Analyse van den onregelmatigen Pols. III. Over eenige Vormen van Allorhythmie en Bradykardie. *Nederlandsch Tijdschrift voor Geneeskunde, Amsterdam* **2**: 1132.

3 Wolff L, Parkinson J, White PD (1930). Bundle-branch block with short P–R interval in healthy young people prone to paroxysmal tachyarrhythmia. *Am Heart J St Louis* **5**: 685.

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- Cardiac tamponade: management 780

Adult basic life support

Basic life support (BLS) is the backbone of effective resuscitation following a cardiorespiratory arrest. The aim is to maintain adequate ventilation and circulation until the underlying cause for the arrest can be reversed. 3–4 minutes without adequate perfusion (less if the patient is hypoxic) will lead to irreversible cerebral damage. The usual scenario is an unresponsive patient found by staff, who alert the cardiac arrest team. The initial assessment described below should have already been performed by the person finding the patient. The same person should have also started cardiopulmonary resuscitation (CPR). Occasionally you will be the first to discover the patient, and it is important to rapidly assess the patient and begin CPR. The various stages in basic life support are described here and summarized in Fig. 17.1.

1. Assessment of the patient

- *Ensure safety of rescuer and victim*
- *Check whether the patient is responsive.* Gently shake victim and ask loudly '**are you all right?**'
 - (a) If victim responds, place him/her in the recovery position and get help.
 - (b) If victim is unresponsive, shout for help and move on to assess airway (see below).

2. Airway assessment

- *Open the airway.* With two fingertips under the point of the chin, tilt the head up. If this fails, place your fingers behind the angles of the lower jaw and apply steady pressure upwards and forwards. Remove ill-fitting dentures and any obvious obstruction. If the patient starts breathing, roll the patient over into the recovery position and try to keep the airway open until an oropharyngeal airway can be inserted.
- *Keep airway open, look, listen, and feel for breathing.* Look for chest movements, listen at the victim's mouth for breathing sounds and feel for air on your cheek (for no more than 10 seconds).
 - (a) If patient is breathing, turn them into the recovery position, check for continued breathing and get help.
 - (b) If patient is not breathing, making occasional gasps, or weak attempts at breathing, send someone (or go for help if alone). (On return) start rescue breaths by giving two slow effective breaths, each resulting in a visible rise and fall in the chest wall.

3. Assessment of circulation

- *Assess signs of circulation by feeling the carotid pulse for no more than 10 s.*
 - (a) If there are signs of circulation but no breathing, continue rescue breaths and check for signs of breathing every 10 breaths (approximately one breath a minute).
 - (b) If there are no signs of circulation start chest compression at a rate of 100 times per minute. Combine rescue breaths and compression at the rate of 15 compressions to two effective breaths.
- *The ratio of compressions to lung inflation remains the same for resuscitation with two persons.*

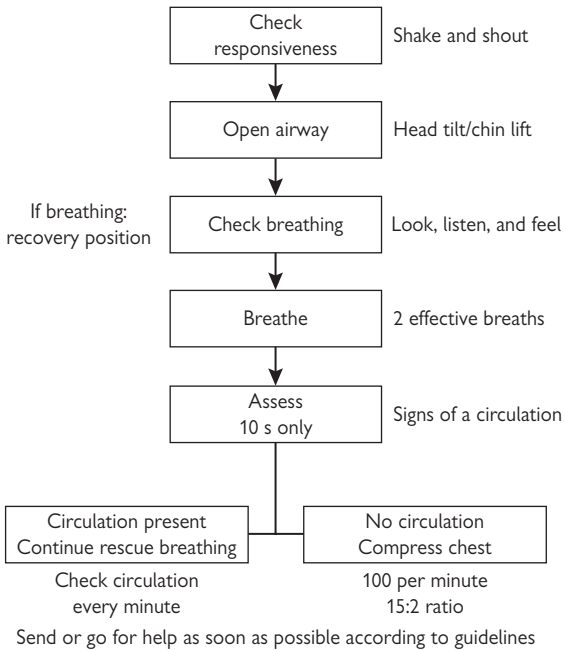



Fig. 17.1 Adult basic life support. For further information see The Resuscitation Council (UK) website <http://www.resus.org.uk/>.

Adult advanced life support

- It is unlikely that an effective spontaneous cardiac activity will be restored by basic life support without more advanced techniques (intubation for effective ventilation, drugs, defibrillation, etc.). Do not waste time. As soon as help arrives, delegate CPR to someone less experienced in advanced cardiac life support (ACLS), so that you are able to continue.
- Attach the patient to a cardiac monitor as soon as possible to determine the cardiac rhythm and treat appropriately (see  Universal treatment algorithm, p. 716).
- Oropharyngeal (Guedel) or nasopharyngeal airways help maintain the patency of the airway by keeping the tongue out of the way. They can cause vomiting if the patient is not comatose. Endotracheal (ET) intubation is the best method of securing the airway. *Do not attempt this if you are inexperienced.* See also Figs. 17.2 and 17.3.
- Establish venous access. Central vein cannulation (internal jugular or subclavian) is ideal but requires more training and practice, and is not for the inexperienced. If venous access fails, drugs may be given via an ET tube into the lungs (except for bicarbonate and calcium salts). Double the dose of drug if using this route, as absorption is less efficient than IV.

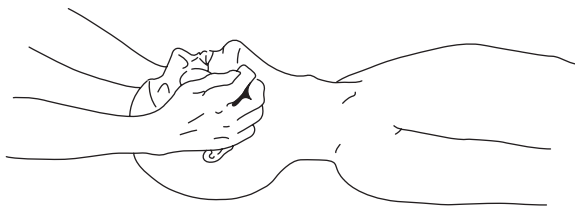
Post-resuscitation care

- Try to establish the events that precipitated the arrest from the history, staff, witnesses, and the hospital notes of the patient. Is there an obvious cause (myocardial infarction (MI), hypoxia, hypoglycaemia, stroke, drug overdose or interaction, electrolyte abnormality, etc.)? Record the duration of the arrest in the notes, with the interventions, drugs (and doses) in chronological order.
- Examine the patient to check both lung fields are being ventilated; check for ribs that may have broken during CPR. Listen for any cardiac murmurs. Check the neck veins. Examine the abdomen for an aneurysm or signs of peritonism. Insert a urinary catheter. Consider a nasogastric (NG) tube if the patient remains unconscious. Record the Glasgow Coma Score and perform a brief neurological assessment.
- Investigations: *electrocardiogram* (ECG) (looking for MI, ischaemia, tall T waves ($\uparrow K^+$)); *arterial blood gases* (ABG) (mixed metabolic and respiratory acidosis is common and usually responds to adequate oxygenation and ventilation once the circulation is restored; if severe, consider bicarbonate); *chest X-ray* (CXR; check position of ET tube, look for pneumothorax); *urea and electrolytes* (U&Es), and *glucose*.
- After early and successful resuscitation from a primary cardiac arrest, the patient may rapidly recover completely. The patient must be transferred to high-dependency unit (HDU) or coronary care unit (CCU) to monitor for 12–24 h. Commonly the patient is unconscious post-arrest and should be transferred to the intensive therapy unit (ITU) for mechanical ventilation and haemodynamic monitoring and support for ≥ 24 hours.

- Change any venous lines that were inserted at the time of arrest for central lines inserted with sterile technique. Insert an arterial line and consider a pulmonary artery (PA) catheter (Swan–Ganz) if requiring inotropes.
- Remember to talk to the relatives. Keep them informed of events and give a realistic (if bleak) picture of the arrest and possible outcomes.
- When appropriate, consider the possibility of organ donation and do not be frightened to discuss this with the relatives. Even if discussion with the relatives is delayed, remember corneas and heart valves may be used up to 24 hours after death.

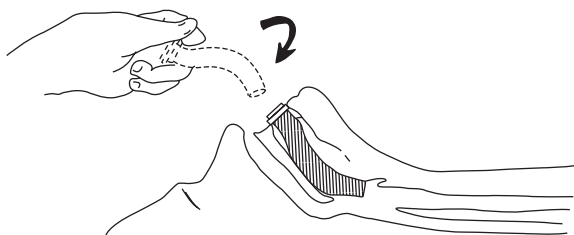


Jaw lift to open the airway

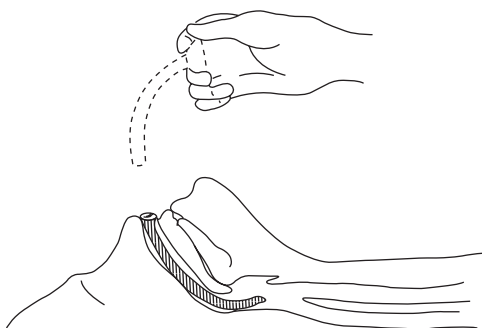


Jaw thrust (thrust the angle of the mandible upwards)

Fig. 17.2 Opening airways. Reproduced with permission from Ramrakha P, Moore K, Sam M (2010). *Oxford Handbook of Acute Medicine*, 3rd ed. Oxford: Oxford University Press.



Insertion of oropharyngeal airway



Insertion of nasopharyngeal airway

Fig. 17.3 Insertion of nasopharyngeal airway. Reproduced with permission from Ramrakha P, Moore K, Sam M (2010). *Oxford Handbook of Acute Medicine*, 3rd ed. Oxford: Oxford University Press.

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Universal treatment algorithm

- Cardiac rhythms of cardiac arrest can be divided into two groups:
 1. *ventricular fibrillation/pulseless ventricular tachycardia (VF/VT)*
 2. *other cardiac rhythms*, which include asystole and *pulseless electrical activity (PEA)*.
- The principal difference in treatment of the two groups of arrhythmias is the need for attempted defibrillation in the VF/VT group of patients.
- Fig. 17.4 summarizes the algorithm for management of both groups of patients.

VF/VT

- VF/VT are the most common rhythms at the time of cardiac arrest.
- Success in treatment of VF/VT is dependent on the delivery of prompt defibrillation. With each minute, the chances of successful defibrillation decline by 7–10%.
- *Precordial thump*: if arrest is witnessed or monitored, a sharp blow with a closed fist on the patient's sternum may convert VF/VT back to a perfusing rhythm. It is particularly effective if delivered within 30 s after cardiac arrest.
- Shock cycles are generally in groups of three. Initially 200 J, 200 J, and 360 J, with subsequent cycles at 360 J.
- After each shock (or sequence), the carotid pulse should be palpated only if the waveform changes to one usually capable of providing a cardiac output.
- The shock cycle is repeated every minute if VF/VT persists.
- Myocardial and cerebral viability must be maintained after each shock cycle, with chest compressions and ventilation.
- In between cycles of defibrillation, reversible factors must be identified and corrected, the patient intubated (if possible) and venous access obtained.
- Adrenaline should be given every 3 minutes (1 mg IV and 2–3 mg via endotracheal route).

Non-VF/VT rhythms

- The outcome from these rhythms is generally worse than VF/VT unless a reversible cause can be identified and treated promptly.
- Chest compressions and ventilation should be undertaken for three minutes with each loop of the algorithm (1 min if directly after a shock).
- With each cycle, attempts must be made to intubate the patient, gain IV access and give adrenaline.

Asystole

- Atropine 3 mg IV should be given to block all vagal output.
- In the presence of P waves on the ECG strip/monitor, pacing (external or transvenous) must be considered.

PEA

- Identification of the underlying cause and its correction are both vital for successful resuscitation. Resuscitation must be continued while reversible causes are being sought.

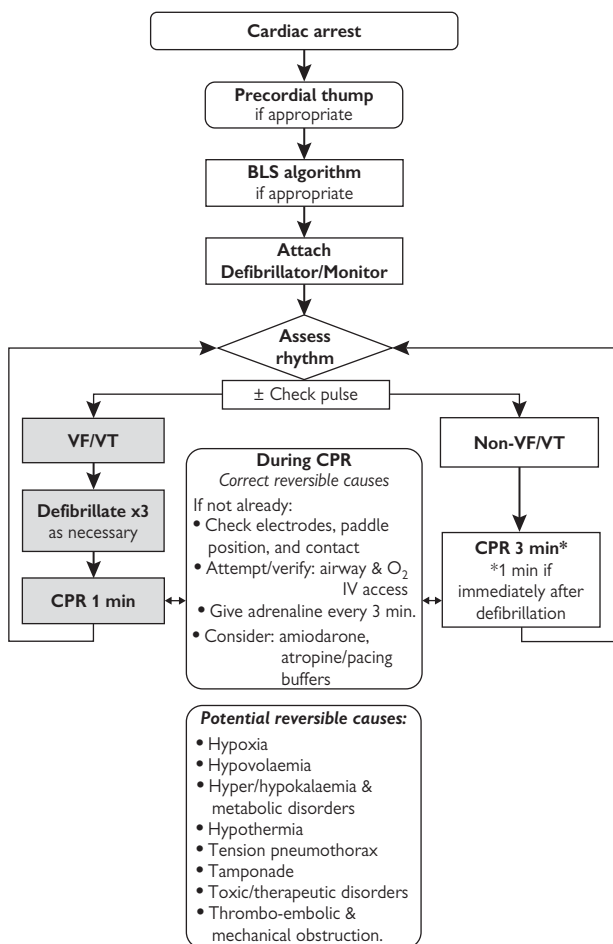


Fig. 17.4 The advanced life support universal algorithm for the management of cardiac arrest in adults. For further information see The Resuscitation Council (UK) website <http://www.resus.org.uk/>.

Primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction (see p. 268)

- Primary percutaneous coronary intervention (PCI) is the current gold standard reperfusion strategy for treatment of ST-segment elevation MI (STEMI).
- Primary PCI requires significant coordination between the emergency services, community hospitals, and invasive centres. It must only be performed if: (1) a primary PCI programme is available; (2) the patient presents to an invasive centre and can undergo catheterization without delay.

Indication for primary PCI

- All patients with chest pain and ST-segment elevation or new left bundle branch block (LBBB) fulfil primary PCI criteria (compare with indications for thrombolysis).
- This will include a group of patients where ST-segment elevation may not fulfil thrombolysis criteria.
- In general, patients in whom thrombolysis is contraindicated should be managed by primary PCI. Cases where there is significant risk of bleeding must be managed individually.

Acute MI: thrombolysis protocol

See Fig. 17.5.

Typical cardiac chest pain

Within 12 hours of onset

Typical ECG changes

ST elevation ≥ 1 mm in ≥ 2 contiguous leads
Or New LBBB

Contraindications to thrombolysis

- Internal bleed/surgery/injury/organ biopsy trauma/dental extraction ~ 2 weeks
- Any haemorrhagic CVA
- Other CVA, neurosurgery, head injury < 2 weeks
- Know or suspected active peptic ulcer
- Pregnancy
- Any history of bleeding disorder or warfarin (INR > 4.0)

Management of high BP:

- If systolic BP > 180 mmHg
or
- If diastolic BP > 110 mmHg

Reduce with IV nitrates start at 2 ml/hr.

Thrombolysate immediately once BP $< 180/110$

Heparin bolus
5000 units
followed by
1st dose reteplase
Exactly 30 minutes
later give
2nd dose reteplase
Followed by
Heparin infusion

**Anterior MI: Age ~ 75 yrs:
 < 6 hrs pain onset**

**New LBBB: Age ~ 75 yrs:
 < 6 hrs pain onset**

Systolic BP < 90

**Previously had
Streptokinase**

Admit to CCU

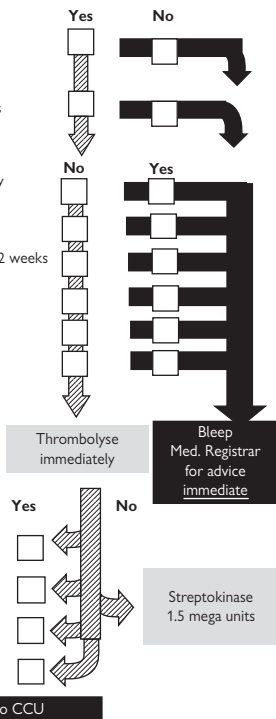


Fig. 17.5 Acute MI: thrombolysis protocol. BP = blood pressure; CVA = cerebrovascular accident; INR = international normalized ratio.

Acute myocardial infarction

- 📖 ST elevation myocardial infarction (STEMI) p. 256
- 📖 STEMI: diagnosis p. 258
- 📖 STEMI: general measures p. 262
- 📖 STEMI: reperfusion therapy (thrombolysis) p. 264
- 📖 STEMI: reperfusion by primary PCI p. 268
 - 📖 Rescue PCI p. 269
- 📖 STEMI: additional measures p. 270
- 📖 Right ventricular (RV) infarction p. 272
- 📖 STEMI: pre-discharge risk stratification p. 274
- 📖 STEMI: complications p. 276
- 📖 Ventricular septal defect post-MI p. 278
- 📖 Acute mitral regurgitation post-MI p. 280
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- 📖 Cocaine-induced MI p. 282
- 📖 Ventricular tachyarrhythmias post-MI p. 284
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- 📖 Bradyarrhythmias and indications for pacing p. 285
- 📖 Bradyarrhythmias post-MI p. 285
- 📖 Hypotension and shock post-MI p. 286
- 📖 Non-ST elevation myocardial infarction (NSTEMI)/unstable angina (UA) p. 290

Treatment options in tachyarrhythmias

Sinus tachycardia	Look for cause	β -blockade if anxious	
Atrial fibrillation	<i>Rate control</i>	<i>Version to sinus rhythm (SR)</i>	<i>Prevention</i>
Atrial flutter	<i>(atrioventricular (AV) node)</i>		
Supraventricular tachycardia (SVT) (📖 p. 494)	<ul style="list-style-type: none"> • Digoxin • β-blockade • calcium blocker (e.g. verapamil) 	<ul style="list-style-type: none"> • Flecainide • Amiodarone • Sotalol • Disopyramide • Synchronized DC shock 	<ul style="list-style-type: none"> • Amiodarone • Sotalol • Quinidine • Procainamide
Junctional tachycardia (atrioventricular nodal re-entrant tachycardia (AVNRT)) (📖 p. 498)	<ul style="list-style-type: none"> • Adenosine • β-blockade • Verapamil • (Vagal stimulation) 	<ul style="list-style-type: none"> • Digoxin • Flecainide • Synchronized DC shock 	
Accessory pathway tachycardias (i.e. atrioventricular re-entry tachycardia (AVRT)) (📖 p. 498)	<i>At AV node</i>	<i>At accessory pathway</i>	<i>Termination only</i>
	<ul style="list-style-type: none"> • Adenosine • β-blockade 	<ul style="list-style-type: none"> • Sotalol • Flecainide • Disopyramide • Quinidine • Amiodarone 	<ul style="list-style-type: none"> • Synchronized DC shock
Ventricular tachycardia (📖 p. 508)	<i>Termination and prevention</i>		<i>Termination only</i>
	<ul style="list-style-type: none"> • Lidocaine • Procainamide • Amiodarone • Magnesium 	<ul style="list-style-type: none"> • Flecainide • Disopyramide • Propafenone • β-blockade 	<ul style="list-style-type: none"> • DC shock

Ventricular tachycardia: drugs

See Table 17.1.

Table 17.1 Dosages of selected antiarrhythmics for the acute treatment of VT

Drug	Dosage
Magnesium sulphate	<i>Loading dose</i> 8 mmol (2g) IV over 2–15 min (repeat once if necessary) <i>Maintenance dose</i> 60 mmol/48 mL saline at 2–3 mL/h
Lidocaine	<i>Loading dose</i> 100 mg IV over 2 min (repeat once if necessary) <i>Maintenance dose</i> 4 mg/min for 30 min 2 mg/min for 2 h 1–2 mg/min for 12–24 h
Procainamide	<i>Loading dose</i> 100 mg IV over 2 min Repeat every 5 min to max 1 g <i>Maintenance dose</i> 2–4 mg/min IV infusion 250 mg q6h PO
Amiodarone	<i>Loading dose</i> 300 mg IV over 60 min via central line followed by 900 mg IV over 23 h or 200 mg PO tds x 1 week then 200 mg PO bd x 1 week <i>Maintenance dose</i> 200–400 mg od IV or PO
Disopyramide	<i>Loading dose</i> 50 mg IV over 5 min repeated every 5 min up to maximum 150 mg IV 200 mg PO <i>Maintenance dose</i> 2–5 mg/min IV infusion 100–200 mg q6h PO
Flecainide	<i>Loading dose</i> 2 mg/kg IV over 10 min (max 150 mg) <i>Maintenance dose</i> 1.5 mg/kg IV over 1 hour then 100–250 mcg/kg/h IV for 24 h or 100–200 mg PO bd

Supraventricular tachyarrhythmias

See Table 17.2.

Table 17.2 Dosages of selected antiarrhythmics for SVT

Drug	Dosage
Digoxin	<i>Loading dose:</i> IV 0.75–1 mg in 50 mL saline over 1–2 h PO 0.5 mg q12h for 2 doses then 0.25 mg q12h for 2 days <i>Maintenance dose:</i> 0.0625–0.25 mg daily (IV or PO)
Propranolol	IV 1 mg over 1 min, repeated every 2 min up to maximum 10 mg PO 10–40 mg 3–4 times a day
Atenolol	IV 5–10 mg by slow injection PO 25–100 mg daily
Sotalol	IV 20–60 mg by slow injection PO 80–160 mg bd
Verapamil	IV 5 mg over 2 min; repeated every 5 min up to maximum 20 mg PO 40–120 mg tds
Procainamide	IV 100 mg over 2 min; repeated every 5 min up to maximum 1 g PO 250 mg q6h
Amiodarone	<i>Loading dose:</i> IV 300 mg over 60 min via central line followed by 900 mg IV over 23 h or PO 200 mg tds x 1 week then 200 mg PO bd x 1 week <i>Maintenance dose:</i> 200–400 mg od IV or PO
Disopyramide	IV 50 mg over 5 min; repeated every 5 min up to maximum 150 mg IV 100–200 mg q6h PO
Flecainide	2 mg/kg IV over 10 min (max 150 mg) or 100–200 mg PO bd

Acute pulmonary oedema: assessment

Presentation

- Acute breathlessness, cough, frothy blood-stained (pink) sputum
- Collapse, cardiac arrest, or shock
- Associated features may reflect underlying cause:
 - chest pain or palpitations—? ischaemic heart disease (IHD)/MI, arrhythmia
 - preceding history of dyspnoea on exertion—? IHD, poor left ventricular (LV) function
 - oliguria, haematuria—? acute renal failure
 - seizures, signs of intracranial bleed.

Causes

A diagnosis of pulmonary oedema or 'heart failure' is not adequate. An underlying cause must be sought in order to direct treatment appropriately. Causes may be divided into:

- increased pulmonary capillary pressure (hydrostatic)
- increased pulmonary capillary permeability
- decreased intravascular oncotic pressure.

Often there is a combination of factors involved (e.g. pneumonia, hypoxia, cardiac ischaemia); see [☞ Drugs for hypertensive emergencies, p. 760](#).

The main differential diagnosis is acute (infective) exacerbation of chronic obstructive pulmonary disease (COPD) (previous history, quiet breath sounds \pm wheeze, fewer crackles). It may be difficult to differentiate the two clinically.

Principles of management

1. Stabilize the patient—relieve distress and begin definitive treatment.
2. Look for an underlying cause.
3. Address haemodynamic and respiratory issues.
4. Optimize and introduce long-term therapy.

Initial rapid assessment

- If the patient is very unwell (e.g. unable to speak, hypoxic, systolic BP <100 mmHg), introduce stabilizing measures and begin treatment immediately before detailed examination and investigations (see [☞ Pulmonary oedema: management, p. 728](#)).
- If the patient is stable and/or if there is doubt as to the diagnosis, give oxygen and diuretic, but await the outcome of clinical examination and CXR before deciding on definitive treatment.

Urgent investigations for all patients

- ECG
 - Sinus tachycardia most common
 - ? any cardiac arrhythmia (atrial fibrillation (AF), SVT, VT)
 - ? evidence of acute ST change (STEMI, NSTEMI, unstable angina (UA))
 - ? evidence of underlying heart disease (left ventricular hypertrophy (LVH), p mitrale)

● CXR	● To confirm the diagnosis, looking for interstitial shadowing, enlarged hila, prominent upper lobe vessels, pleural effusion, and Kerley B lines. Cardiomegaly may or may not be present. Also exclude pneumothorax, pulmonary embolus (oligaemic lung fields), and consolidation
● ABG	● Typically ↓ P_aO_2 . P_aCO_2 levels may be ↓ (hyperventilation) or ↑ depending on the severity of pulmonary oedema. Pulse oximetry may be inaccurate if peripherally shut down
● U&Es	● ? pre-existing renal impairment. Regular K^+ measurements (once on IV diuretics)
● Full blood count (FBC)	● ? anaemia or leucocytosis, indicating the precipitant
● Echocardiography (ECHO)	● As soon as practical to assess LV function, valve abnormalities, ventricular septal defect (VSD), or pericardial effusion

P_aCO_2 = partial pressure of carbon dioxide in the arterial blood; P_aO_2 = partial pressure of oxygen in the arterial blood.

Investigations for patients with pulmonary oedema

All patients should have:

- FBC, U&Es, C-reactive protein (CRP)
- serial biochemical markers of myocardial injury (creatine kinase (CK), CK-MB, troponins)
- liver function tests (LFTs), albumin, total protein
- ECG
- CXR
- ECHO (± transoesophageal echocardiography (TOE))
- arterial blood gases.

Where appropriate, consider:

- septic screen (sputum, urine, blood cultures)
- Holter monitor (?arrhythmias)
- coronary angiography (?IHD)
- right and left heart catheter (if ECHO is unable to provide adequate information on pressures, shunts, valve disease)
- endomyocardial biopsy (myocarditis, infiltration)
- multigated acquisition (MUGA) scan
- cardiopulmonary exercise test with an assessment of peak oxygen consumption.

Pulmonary oedema: causes

Look for an underlying cause for pulmonary oedema.

Increased pulmonary capillary pressure (hydrostatic)

Left atrial pressure	<ul style="list-style-type: none"> • Mitral valve disease • Arrhythmia (e.g. AF) with pre-existing mitral valve disease • Left atrial myxoma
Left ventricular end-diastolic pressure (LVEDP)	<ul style="list-style-type: none"> • Ischaemia • Arrhythmia • Aortic valve disease • Cardiomyopathy • Uncontrolled hypertension • Pericardial constriction • Fluid overload • High-output states (anaemia, thyrotoxicosis, Paget's, AV fistula, beri-beri) • Reno vascular disease.
Pulmonary venous pressure	<ul style="list-style-type: none"> • L → R shunt (e.g. VSD) • Venocclusive disease.
Neurogenic	<ul style="list-style-type: none"> • Intracranial haemorrhage • Cerebral oedema • Post-ictal

High-altitude pulmonary oedema

Increased pulmonary capillary permeability

Acute lung injury	<ul style="list-style-type: none"> • Acute respiratory distress syndrome (ARDS)
-------------------	--

Decreased intravascular oncotic pressure



Hypoalbuminaemia	<ul style="list-style-type: none"> • ↑ Losses (e.g. nephrotic syndrome, liver failure) • ↓ Production (e.g. sepsis) • Dilution (e.g. crystalloid transfusion)
------------------	--


Note: the critical LA pressure for hydrostatic oedema = serum albumin (g/L) × 0.57.

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Pulmonary oedema: management




Stabilize the patient

- Patients with acute pulmonary oedema should initially be continuously monitored and managed where full resuscitation facilities are available.
- Sit the patient up in bed.
- Give 60–100% oxygen by face mask (unless contraindicated, COPD).
- If the patient is severely distressed, summon the 'on-call' anaesthetist and inform ITU. If dyspnoea cannot be significantly improved by acute measures (below) the patient may require continuous positive airways pressure (CPAP) or mechanical ventilation.
- Treat any haemodynamically unstable arrhythmia (urgent synchronized DC shock may be required (see  DC cardioversion, p. 818).
- Give:
 - diamorphine 2.5–5 mg IV (caution abnormal ABGs)
 - metoclopramide 10 mg IV
 - furosemide 40–120 mg slow IV injection.
- Secure venous access and send blood for urgent U&Es, FBC, and cardiac enzymes (including troponin).
- Unless thrombolysis is indicated, take ABG.
- If the systolic blood pressure is ≥ 90 mmHg and the patient does not have aortic stenosis:
 - give sublingual glyceryl trinitrate (GTN) spray (2 puffs)
 - start IV GTN infusion 1–10 mg/h, increase the infusion rate every 15–20 minutes, titrating against blood pressure (aiming to keep systolic BP ~ 100 mmHg).
- If the systolic blood pressure is < 90 mmHg, treat patient as cardiogenic shock (see  NSTEMI/UA: invasive versus non-invasive strategies, p. 301).
- Insert a urinary catheter to monitor urine output.
- Repeat ABG and K^+ if the clinical condition deteriorates/fails to improve, or after 2 h if there is improvement and the original sample was abnormal.
- Monitor pulse, BP, respiratory rate, O_2 saturation with a pulse oximeter (if an accurate reading can be obtained), and urine output.

If the patient responds arrange appropriate investigations as listed on  Acute pulmonary oedema: assessment, p. 724 to help with further management. However, if there is further deterioration, specific measures should be taken to address problems.

Further management

The subsequent management of the patient is aimed at ensuring adequate ventilation/gas exchange and haemodynamic stability and correcting any reversible precipitants of acute pulmonary oedema.

- Assess the patient's respiratory function:
 - does the patient require respiratory support?
- Assess the patient's haemodynamic status (see  Cardiogenic shock, p. 288):
 - is the patient in shock (see  Cardiogenic shock, p. 288).
- Look for an underlying cause (see  Pulmonary oedema: causes, p. 726).

- Conditions that require specific treatment:
 - acute aortic and mitral regurgitation
 - diastolic LV dysfunction
 - fluid overload
 - renal failure
 - severe anaemia
 - hypoproteinaemia.

If the patient remains unstable and/or deteriorates, assess their respiratory function.

Assessment of respiratory function

- Wheeze may be caused by interstitial pulmonary oedema. If there is a history of asthma, give nebulized salbutamol (2.5–5 mg), nebulized ipratropium bromide (500 mcg), and hydrocortisone (200 mg) IV. Consider commencing aminophylline infusion. This will relieve bronchospasm, as well as 'off-load' by systemic vasodilatation. However, it may worsen tachycardia, and can be arrhythmogenic and lower K^+ (supplement to ensure K^+ 4–5 mmol/L).
- *Indications for further respiratory support* include:
 - patient exhaustion or continuing severe breathlessness
 - persistent $P_aO_2 < 8$ kPa
 - rising P_aCO_2
 - persistent or worsening acidosis ($pH < 7.2$).
- CPAP: this may be tried for co-operative patients, who can protect their airway, and have adequate respiratory muscle strength and who are not hypotensive. The positive pressure reduces venous return to the heart and may compromise BP.
- *Endotracheal intubation and mechanical ventilation* may be required, and some positive end-expiratory pressure (PEEP) should be used.
- Discuss the patient with the on-call anaesthetist or ITU team early.

Assess the patient's haemodynamic status

It is important to distinguish between cardiogenic and non-cardiogenic pulmonary oedema, as further treatment is different between the two groups. This may be difficult clinically. A PA (Swan–Ganz) catheter must be inserted if the patient's condition will allow.

- *Non-cardiogenic pulmonary oedema* occurs when the hydrostatic pressure within the capillary system exceeds the plasma oncotic pressure. In patients with hypoalbuminaemia this will occur at a pulmonary capillary wedge pressure (PCWP) < 15 mmHg. The critical PCWP may be estimated by $\text{serum albumin (g/L)} \times 0.57$. Thus, a patient with a serum albumin of 15 g/L will develop hydrostatic pulmonary oedema at a LA pressure of 8 mmHg; a serum albumin of 30 g/L will require an LA pressure of > 17 mmHg, and so on . . .
- *Cardiogenic pulmonary oedema* is often associated with significant systemic hypotension or low-output states. Contributing factors include conditions where there is 'mechanical' impairment to forward flow (e.g. valvular heart disease (especially if acute), VSD), or severe myocardial disease (large MI, ongoing ischaemia, acute myocarditis, cardiomyopathy).

- The gradient between PA diastolic pressure (PAD) and PCWP (PAD – PCWP) is generally <5 mmHg in cardiogenic and >5 mmHg in non-cardiogenic pulmonary oedema (e.g. ARDS).
- The pulse and BP are most commonly elevated due to circulating catecholamines and overactivity of the renin–angiotensin system (RAS). Examination reveals sweating, cool ‘shut-down’ peripheries, high pulse volume (assess carotid or femoral pulses).

Management

The general approach involves combination of diuretics, vasodilators ± inotropes. Patients may be divided into two groups:

- patients in shock (with systolic BP <100 mmHg)—see [Pulmonary oedema: management](#), p. 728
- haemodynamically stable patients with systolic BP >100 mmHg—(see [Pulmonary oedema](#), p. 726–733).

Patients with systolic BP <100 mmHg

- The patient is in incipient (or overt) shock. The most common aetiology is cardiogenic shock but remember non-cardiogenic causes (e.g. ARDS, septic shock).
- *Optimal monitoring and access:* central line ± PA catheter (Swan–Ganz), urinary catheter, arterial line (monitoring BP and ABG). Internal jugular lines are preferable, as the risk of pneumothorax is lower.
- Ensure the patient is not underfilled, using PCWP as a guide (<10 mmHg) (mistaken diagnosis e.g. septic shock from bilateral pneumonia).
- *Is there a mechanical cause that may require emergency surgery?*
 - Arrange an urgent ECHO to rule out:
 - VSD and acute mitral regurgitation (MR) in all patients with recent MI with/without new murmur (see [Ventricular septal defect post-MI](#), p.278; [Acute mitral regurgitation post-MI](#), p.280)
 - prosthetic heart valve dysfunction (e.g. dehiscence, infection) or pre-existing native aortic or mitral disease that may require surgery.
 - Discuss the patient early on with cardiologist/cardiac surgeon.

The *choice of inotropic agent* depends on the clinical condition of the patient and, to some extent, the underlying diagnosis:

- *Systolic BP 80–100 mmHg and cool peripheries:* start *dobutamine infusion* at 5 mcg/kg/min, increasing by 2.5 mcg/kg/min every 10–15 minutes to a maximum of 20 µg/kg/min until BP >100 mmHg. This may be combined with dopamine (2.5–5 mcg/kg/min). However, tachycardia and/or hypotension secondary to peripheral vasodilation may limit its effectiveness. *Phosphodiesterase inhibitors* (enoximone or milrinone) should be considered where dobutamine fails.
- *Systolic BP <80 mmHg:* give a slow IV bolus of *adrenaline* (2–5 mL of 1 in 10 000 solution Minijet®) and repeat if necessary.
 - *Dopamine* at doses of >2.5 µg/kg/min has a pressor action in addition to direct and indirect inotropic effects and may be used at higher doses (10–20 mcg/kg/min) if the blood pressure remains low. However, it tends to raise the pulmonary capillary filling pressure further and should be combined with vasodilators (e.g. nitroprusside

or hydralazine) once the blood pressure is restored (see below). Beware of arrhythmias at these doses.

- *Adrenaline* infusion may be preferred to high-dose dopamine as an alternative inotrope. Once the blood pressure is restored (>100 mmHg), vasodilators such as nitroprusside/hydralazine or GTN infusion should be added to counteract the pressor effects. Adrenaline can be combined with dobutamine and/or a phosphodiesterase inhibitor, especially in the context of a poor ventricle.
- *Intra-aortic balloon counter pulsation* should also be used with/without inotropes in the context of a potentially reversible cause for the pulmonary oedema and shock (e.g. ongoing myocardial ischaemia, VSD, acute MR).
- Further doses of diuretic may be given.

Patients with systolic BP \geq 100 mmHg

- Further doses of diuretic may be given (furosemide 40–80 mg IV q3–4h or as a continuous infusion (20–80 mg/h)).
- Continue the GTN infusion, increasing the infusion rate every 15–20 min up to 10 mg/h, titrating against blood pressure (aiming to keep systolic BP \sim 100 mmHg).
- Angiotensin-converting enzyme inhibitors (ACE-Is) can be used if BP is adequate and there are no other known contraindications (e.g. RAS, renal failure). Arteriolar vasodilators (nitroprusside or hydralazine) may also be added in or used instead of GTN (\pm ACE-I) in patients with adequate BP. Arterial pressure should be monitored continuously via an arterial line to prevent inadvertent hypotension.

Long-term management

- Unless a contraindication exists, start an ACE-I, increasing the dose to as near the recommended maximal dose as possible. In the context of LV impairment, ACE-Is have significant prognostic benefit.
- If ACE-Is are contraindicated or not tolerated, consider the use of hydralazine and long-acting oral nitrate in combination.
- If the patient is already on high doses of diuretics and ACE-Is, consider the addition spironolactone (25–50 mg) (NB: monitor renal function and serum potassium).
- In the context of stable patients (no clinical features of failure) and poor LV function, β -blockers have significant mortality and some symptomatic benefit (NB: start with a very small dose and increase gradually every 2 weeks with regular monitoring). Bisoprolol, carvedilol, and metoprolol can all be used.
- Ensure all arrhythmias are treated.
- Digoxin can be used for symptomatic improvement.
- Consider multisite pacing (biventricular) in the context of severe LV dysfunction, broad QRS complex \pm MR on ECHO.
- Patients in AF, or with poor LV function should be considered for long-term anticoagulation.
- Patients <60 years with severe irreversible LV dysfunction and debilitating symptoms must be considered for cardiac transplantation.

Pulmonary oedema: specific conditions

Diastolic LV dysfunction

- This typically occurs in elderly hypertensive patients with LV hypertrophy, where there is impaired relaxation of the ventricle in diastole. There is marked hypertension, pulmonary oedema, and normal, or only mild, systolic LV impairment.
- With tachycardia, diastolic filling time shortens. As the ventricle is 'stiff' in diastole, LA pressure is increased and pulmonary oedema occurs (exacerbated by AF, as filling by atrial systole is lost).
- Treatment involves control of hypertension with IV nitrates (and/or nitroprusside), calcium-channel blockers (verapamil or nifedipine) and even certain β -blockers (e.g. carvedilol, bisoprolol).

Fluid overload

- Standard measures are usually effective.
- In extreme circumstances, venesection may be necessary.
- Check the patient is not anaemic (haemoglobin (Hb) ≥ 10 g/dL). Remove 500 mL blood via a cannula in a large vein and repeat if necessary.
- If anaemic (e.g. renal failure) and acutely unwell, consider dialysis.

Known (or unknown) renal failure

- Unless the patient is permanently anuric, large doses of IV furosemide may be required (up to 1 g given at 4 mg/min) in addition to standard treatment.
- If this fails, or the patient is known to be anuric, dialysis will be required.
- In patients not known to have renal failure, an underlying cause should be sought.

Anaemia


- Cardiac failure may be worsened or precipitated by the presence of significant anaemia. Symptoms may be improved in the long term by correcting this anaemia.
- Generally, transfusion is unnecessary with Hb > 9 g/dL unless there is a risk of an acute bleed. Treatment of pulmonary oedema will result in haemoconcentration and a 'rise' in the Hb.
- If the anaemia is thought to be exacerbating pulmonary oedema, ensure that an adequate diuresis is obtained prior to transfusion. Give slow transfusion (3–4 h per unit) of packed cells, with IV furosemide 20–40 mg before each unit.

Hypoproteinaemia

- The critical left atrial (LA) pressure at which hydrostatic pulmonary oedema occurs is influenced by the serum albumin and approximates to serum albumin concentration (g/L) \times 0.57.
- Treatment involves diuretics, cautious albumin replacement, spironolactone (if there is secondary hyperaldosteronism), and treatment of the underlying cause for hypoproteinaemia.

Acute aortic regurgitation

Presentation

- Sudden, severe aortic regurgitation (AR) presents as cardiogenic shock and acute pulmonary oedema.
- The haemodynamic changes are markedly different from those seen in chronic AR. The previous normal-sized LV results in a smaller effective forward flow and higher LVEDP for the same degree of AR.
- Patients are often extremely unwell, tachycardic, peripherally shut down, and frequently have pulmonary oedema. Unlike chronic AR, pulse pressure may be near normal.
- If available, ask for a history of previous valvular heart disease, hypertension, features of Marfan syndrome, and risk factors for infective endocarditis.
- Physical signs of severe AR include a quiet aortic closure sound (S_2); an ejection systolic murmur over the aortic valve (turbulent flow); high-pitched and short, early diastolic murmur (AR); quiet S_1 (premature closure of the mitral valve (MV)).
- Examine specifically for signs of an underlying cause (see  Aortic regurgitation, p. 170).
- Where there is no obvious underlying cause (e.g. acute MI), assume infective endocarditis until proven otherwise.

Causes

- Infective endocarditis
- Ascending aortic dissection
- Collagen vascular disorders (e.g. Marfan)
- Connective tissue diseases (large and medium vessel arteritis)
- Trauma
- Dehiscence of a prosthetic valve.

Diagnosis

Diagnosis is based on a combination of clinical features and transthoracic and/or transoesophageal ECHO.


Management

Acute AR is a surgical emergency and all other management measures are only aimed at stabilizing the patient until urgent aortic valve replacement (AVR) can take place. The patient's clinical condition will determine the urgency of surgery (and mortality). Liaise immediately with local cardiologists.

General measures (see  Pulmonary oedema: management, p. 728)

- Admit the patient to intensive care or medical HDU.
- Give oxygen, and begin treating any pulmonary oedema with diuretics.
- Monitor blood gases; mechanical ventilation may be necessary.
- Blood cultures x3 are essential.
- Serial ECG: watch for developing AV block or conduction defects.

Specific measures

- Every patient must be discussed with the regional cardiothoracic centre.
- In the context of good systemic BP, vasodilators such as sodium nitroprusside or hydralazine may temporarily improve forward flow and relieve pulmonary oedema.
- Inotropic support may be necessary if the patient is hypotensive. However, inotropes are best avoided, as any increase in systemic pressures may worsen AR.
- All patients with haemodynamic compromise should have immediate or urgent AVR.
- Infective endocarditis: indications for surgery are given on  Surgery for endocarditis, p. 202.
- Use of an intra-aortic balloon pump (IABP) must be avoided, as it will worsen AR.

Acute mitral regurgitation

Presentation

- Patients most commonly present with acute breathlessness and severe pulmonary oedema. Symptoms may be less severe, or spontaneously improve as left atrial compliance increases. There may be a history of previous murmur, angina, or MI.
- The signs are different from those seen in chronic mitral regurgitation (MR) because of the presence of a non-dilated, and relatively non-compliant LA. Acute MR results in a large LA systolic pressure wave ('v' wave), and hence pulmonary oedema.
- Patients may be acutely unwell with tachycardia, hypotension, peripheral vasoconstriction and pulmonary oedema, and a pansystolic murmur of MR.
- Later in the illness, probably because of sustained high left atrial and pulmonary venous pressures, right heart failure develops.
- Examine for signs of any underlying conditions.
- The important differential diagnosis is a VSD. Transthoracic ECHO and Doppler studies can readily differentiate between the two conditions. Alternatively, if ECHO not available, pulmonary artery catheterization in acute MR will exclude the presence of a left-to-right shunt, and the PCWP trace will demonstrate a large 'v' wave.
- Where there is no obvious underlying cause (e.g. acute MI), assume the patient has infective endocarditis until proven otherwise.

Diagnosis

Diagnosis is based on a combination of clinical features and ECHO. Transthoracic ECHO can readily diagnose and quantify MR. It also provides information on LV status (in particular, regional wall motion abnormalities, which can give rise to MR). TOE can provide specific information about the aetiology of valve dysfunction, including papillary muscle rupture and MV leaflet (anterior and posterior) structural abnormalities. This information will be vital for a decision regarding definitive management.

General measures (see Pulmonary oedema: management, p. 728)

- Admit the patient to intensive care or medical HDU.
- Give oxygen, and begin treating any pulmonary oedema with diuretics.
- Monitor blood gases; mechanical ventilation may be necessary.
- Blood cultures x3 are essential.
- If present, MI should be treated in the standard manner.

Specific measures

- Pulmonary oedema may be very resistant to treatment.
- In the presence of good BP, reduction in preload (GTN infusion and afterload especially with ACE-Is important. Systemic vasodilators such as hydralazine (12.5–100 mg tds) can also be added in.
- An IABP will help decrease LVEDP and increase coronary blood flow.

- *Patients may require inotropic support.* There are multiple combinations and aetiology of MR, and haemodynamic status, and local policy/expertise should dictate choice of agent.
- CPAP and intubation and positive pressure ventilation are extremely useful and must be considered in all severe and/or resistant cases.
- Haemodynamic disturbance and severe pulmonary oedema in the context of acute MR is a surgical emergency.
- *Infective endocarditis:* indications for surgery are given on 📖 Surgery for endocarditis, p. 202.
- *Post-infarct MR:* management depends upon the patient's condition following resuscitation. Patients who are stabilized may have mitral valve replacement (MVR) deferred because of the risks of surgery in the post-infarct patient. Their preoperative management should consist of diuretics and vasodilators, including ACE-Is if tolerated. Advise patients regarding endocarditis prophylaxis.

Causes of acute mitral regurgitation

- Infective endocarditis
- Papillary muscle dysfunction or rupture (post MI, see 📖 Ventricular septal defect post-MI, p. 278)
- Rupture of chordae tendinae (e.g. infection, myxomatous degeneration, systemic lupus erythematosus (SLE))
- Trauma (to leaflets, papillary muscle, or chordae)
- Prosthetic valve malfunction (e.g. secondary to infection)
- Left atrial myxoma
- Acute rheumatic fever
- Collagen vascular disorders (e.g. Marfan)
- Connective tissue diseases (large and medium vessel arteritis)

Deep vein thrombosis: assessment

Presentation

- Deep vein thrombosis (DVT) is most commonly asymptomatic. Minor leg discomfort or isolated swelling (>65%) in the affected limb are the most common clinical features. Breathlessness or chest pain may be secondary to pulmonary embolism (PE).
- Signs include erythema and swelling of the leg, dilated superficial veins, and calf discomfort on dorsiflexion of the foot (Homan's sign). The thrombus may be palpable as a fibrous cord in the popliteal fossa. Confirm the presence of swelling (>2 cm) by measuring the limb circumference 15 cm above and 10 cm below the tibial tuberosity.
- In all cases of leg swelling, abdominal and rectal (and pelvic in women) examination must be carried out to exclude an abdominal cause.

Risk factors for DVT

Procoagulant states

Congenital

Factor V Leiden

Antithrombin III deficiency

Protein C deficiency

Protein S deficiency

Acquired

Malignant disease (~5%)

Antiphospholipid syndrome

Myeloproliferative disorders

Oral contraceptive pill (especially with factor V Leiden mutation)

Nephrotic syndrome (via renal antithrombin (AT)III losses)

Homocystinuria

Paroxysmal nocturnal haemoglobinuria

Venous stasis

Immobility (e.g. long journeys)

Pelvic mass

Recent surgery

Pregnancy or recent childbirth

Severe obesity

Miscellaneous

Hyperviscosity syndromes

Previous DVT or PE

Family history of DVT/PE

Investigations

- *Venous compression ultrasonography* of the leg veins has largely replaced venography as the investigation of choice. It is quick and non-invasive, with sensitivity and specificity of over 90%, and does not carry the risk of contrast allergy or phlebitis. It can simultaneously assess the extent of proximal progression of the thrombus, in particular extension into pelvic vessels.
- *D-dimers* have a high negative predictive value for DVT. A low clinical probability of DVT and a negative D-dimer does not require further investigation. A positive D-dimer result should be followed by ultrasonography.
- *Venography*: use if results are uncertain and clinical suspicion is high.
- Consider baseline investigations (FBC, U&Es, ECG, CXR, urinalysis, and pulse oximetry (\pm ABG)) on all patients.
- If appropriate, look for an underlying cause:
 - coagulation screen
 - pro-coagulant screen: refer to local screening policy and get haematology advice (e.g. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), proteins C and S, ATIII levels, factor V Leiden mutation, auto-antibody (Ab) screen, immunoglobulins and immunoelectrophoretic strip, anticardiolipin antibody, Ham test, etc.)
 - screen for malignancy: ultrasound \pm computed tomography (CT) (abdomen and pelvis), CXR, liver function tests (LFTs), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), CA-125, CA-19.9, β -HCG (human chorionic gonadotrophin), etc.

Deep vein thrombosis: management

- If there is a high clinical suspicion of DVT (the presence of risk factors and absence of an alternative diagnosis), start empiric anticoagulation with low molecular weight heparin (LMWH). This may be stopped if subsequent investigations are negative.
- *Below-knee DVT*: thrombi limited to the calf have a lower risk of embolization and may be treated with compression stockings and subcutaneous prophylactic doses of LMWH until mobile, to deter proximal propagation of thrombus. A brief period of systemic anticoagulation with LMWH may lessen the pain from below-knee DVT.
- *Above-knee DVT*: thrombi within the thigh veins warrant full anticoagulation with LMWH/unfractionated heparin (UFH), and subsequently warfarin.

Anticoagulation


Heparin

- LMWHs have now superseded UFH for management of both DVT and PE. They require no monitoring on a daily basis and also allow outpatient treatment.
- There must be a period of overlap between LMWH/UFH therapy and anticoagulation with warfarin until INR is within the therapeutic range and stable.
- LMWH is administered primarily as once-daily SC injection, and dosage is determined by patient weight.

Warfarin

- Always anticoagulate with LMWH/UFH before starting warfarin. Protein C (a vitamin K-dependent anticoagulant) has a shorter half-life than the other coagulation factors and levels fall more quickly, resulting in a transient procoagulant tendency.
- If DVT is confirmed, commence warfarin and maintain on LMWH/UFH until INR > 2.
- Anticoagulate (INR 2–2.5) for 3 months.
- If there is recurrent DVT, or the patient is at high-risk of recurrence, consider lifelong anticoagulation.

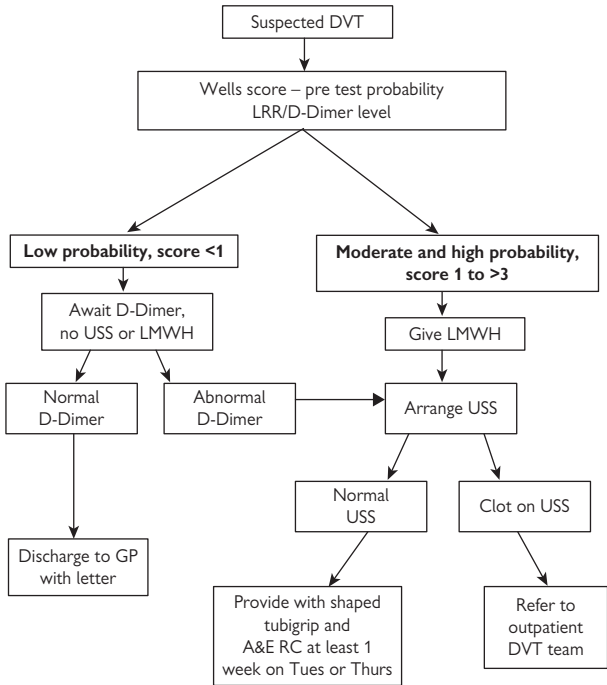
Thrombolysis

- This should be considered for recurrent, extensive, proximal venous thrombosis (e.g. femoral or iliac veins), as it is more effective than anticoagulation alone in promoting clot dissolution, and produces a better clinical outcome.
- Catheter-directed thrombolytic therapy (recombinant tissue plasminogen activator (rt-PA) or streptokinase (SK)) is superior to systemic thrombolysis.
- One approach is streptokinase 250 000 U over 30 min then 100 000 U every hour for 24–72 hours (see data sheet). See  STEMI: reperfusion therapy (thrombolysis), p. 264 for contraindications to thrombolysis.

Further management

- Women taking the combined oral contraceptive pill (OCP) should be advised to stop this.
- If there are contraindications to anticoagulation, consider the insertion of a caval filter to prevent PE.
- All patients should be treated with thigh-high compression stockings to try to reduce symptomatic venous distension when mobilizing.

See Fig 17.6.




Notes

1. Patients who are pregnant or who have previously had a DVT should be in the moderate to high group.
2. Patients who attend after hours should return to the CDU the following morning for a scan. Not all need LMWH.

Fig. 17.6 DVT management algorithm. Reproduced with permission from Ramrakha P, Moore K and Sam, M (2010). *Oxford Handbook of Acute Medicine*, 3rd ed. Oxford: Oxford University Press. A&E RC = ; CDU = ; GP = general practitioner; LRR = ; USS = ultrasound scan.

Pulmonary embolism: assessment

Symptoms

- PE classically presents with sudden-onset, pleuritic chest pain, associated with breathlessness and haemoptysis. Additional symptoms include postural dizziness or syncope.
- Massive PE may present as cardiac arrest (particularly with electromechanical dissociation) or shock.
- Presentation may be atypical, i.e. unexplained breathlessness or unexplained hypotension, or syncope only.
- Pulmonary emboli should be suspected in all breathless patients with risk factors for DVT or with clinically proven DVT (see  Deep vein thrombosis: assessment, p. 738).
- Recurrent PEs may present with chronic pulmonary hypertension and progressive right heart failure.

Signs

- Examination may reveal tachycardia and tachypnoea only. Look for postural hypotension (in the presence of raised jugular venous pressure (JVP)).
- Look for signs of raised right heart pressures and cor pulmonale (raised JVP with prominent 'a' wave, tricuspid regurgitation, parasternal heave, right ventricular (RV) S₃, loud pulmonary closure sound with wide splitting of S₂, pulmonary regurgitation).
- Cyanosis suggests a large pulmonary embolism.
- Examine for a pleural rub (may be transient) or effusion.
- Examine the lower limbs for obvious thrombophlebitis.
- Mild fever (>37.5°C) may be present. There may be signs of co-existing COPD.

Causes

PE is most frequently secondary to DVT (leg >> arm; see  Deep vein thrombosis: assessment, p. 738).

Other causes

- Rarely secondary to right ventricular thrombus (post-MI)
- Septic emboli (e.g. tricuspid endocarditis)
- Fat embolism (post fracture)
- Air embolism (venous lines, diving)
- Amniotic fluid
- Parasites
- Neoplastic cells
- Foreign materials (e.g. venous catheters).

Prognostic features

The prognosis in patients with pulmonary emboli varies greatly, associated in part with any underlying condition. Generally, worse prognosis is associated with larger PE; poor prognostic indicators include:

- hypotension
- hypoxia
- ECG changes (other than non-specific T-wave changes).

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Pulmonary embolism: investigations

See Fig. 17.7.

General investigations

- ABG
 - Normal ABG *does not* exclude a PE.
 - $\downarrow P_aO_2$ (partial pressure of oxygen in arterial blood) is invariable with larger PEs. Other changes include mild respiratory alkalosis and $\downarrow P_aCO_2$ (partial pressure of carbon dioxide in arterial blood; due to tachypnoea), and metabolic acidosis (2° to shock).
- ECG
 - Commonly shows sinus tachycardia \pm non-specific ST- and T-wave changes in the anterior chest leads. The classical changes of acute cor pulmonale such as $S_1Q_3T_3$, right-axis deviation, or right bundle branch block (RBBB) are only seen with massive PE. Less common findings include AF.
- CXR
 - May be normal, and a near-normal chest film in the context of severe respiratory compromise is highly suggestive of a PE. Less commonly, CXR may show focal pulmonary oligoemia (*Westermarck's sign*), a raised hemidiaphragm, small pleural effusion, wedge-shaped shadows based on the pleura, subsegmental atelectasis, or dilated proximal pulmonary arteries.
- Blood tests
 - There is no specific test. FBC may show neutrophil leucocytosis; mildly elevated CK, troponin, and bilirubin may be seen.
- ECHO/TOE
 - Are insensitive for diagnosis but can exclude other causes of hypotension and raised right-sided pressures (e.g. tamponade, RV infarction). In PE they will show RV dilatation and global hypokinesia (with sparing of apex (*McConnell's sign*)), pulmonary artery dilatation and Doppler may show tricuspid/pulmonary regurgitation allowing estimation of RV systolic pressure. Rarely, the thrombus in the pulmonary artery may be visible.

Specific investigations

D-dimer

- A highly sensitive, but non-specific test.
- Useful in ruling out PE in patients with low or intermediate probability.
- Results can be affected by advancing age, pregnancy, trauma, surgery, malignancy, and inflammatory states.

Ventilation/perfusion (V/Q) lung scanning

A perfusion lung scan (with IV technetium-99-labelled albumin) should be performed in all suspected cases of PE. A ventilation scan (inhaled xenon-133) in conjunction increases the specificity by assessing whether

the defects in the ventilation and perfusion scans 'match' or 'mismatch'. Pre-existing lung disease makes interpretation difficult.

- A normal perfusion scan rules out significant-sized PE.
- Abnormal scans are reported as low, medium, or high probability:
 - a high-probability scan is strongly associated with a PE, but there is a significant minority of false positives
 - a low-probability scan with a low clinical suspicion of PE should prompt a search for another cause for the patient's symptoms.

Investigations for an underlying cause for PEs

- Ultrasound scan (USS) of deep veins of the legs
- USS abdomen and pelvis (?occult malignancy/pelvic mass)
- CT abdomen/pelvis
- Screen for inherited procoagulant tendency (e.g. protein C, S, AT III, factor V Leiden, etc.)
- Autoimmune screen (anticardiolipin antibody, antinuclear antibody (ANA))
- Biopsy of suspicious lymph nodes/masses

- if the clinical suspicion of PE is high and the scan is of low or medium probability, alternative investigations are required.

CT pulmonary angiography (CTPA)

- *This is the recommended initial lung imaging modality in patients with non-massive PE.*
- Allows direct visualization of emboli as well as other potential parenchymal disease, which may allow an alternative explanation for symptoms.
- Sensitivity and specificity are high (>90%) for lobar pulmonary arteries but not so high for segmental and subsegmental pulmonary arteries.
- A patient with a positive CTPA does not require further investigation.
- A patient with a negative CTPA in the context of a high/intermediate probability of a PE should undergo further investigation.

Evaluation of leg veins with USS

- Not very reliable. Almost half of patients with PE do not have evidence of a DVT and therefore a negative result cannot rule out a PE.
- Useful second-line investigation as an adjunct to CTPA/VQ scan.
- Outcome studies have demonstrated that it would be safe not to anticoagulate patients with a negative CTPA, and to use lower-limb USS for those with an intermediate/low probability of a PE.

Pulmonary angiography

- Is the 'gold standard' investigation.
- It is indicated in patients in whom diagnosis of embolism cannot be established by non-invasive means. Look for sharp cut-off of vessels or obvious filling defects.
- Invasive investigation and can be associated with 0.5% mortality.
- If there is an obvious filling defect, the catheter or a guide wire passed through the catheter may be used to disobliterate the thrombus.

- After angiography, the catheter may be used to give thrombolysis directly into the affected pulmonary artery (see later).
- The contrast can cause systemic vasodilatation and haemodynamic collapse in hypotensive patients.

MR pulmonary angiography

- Results are comparable to pulmonary angiography in preliminary studies.
- It can simultaneously assess ventricular function.

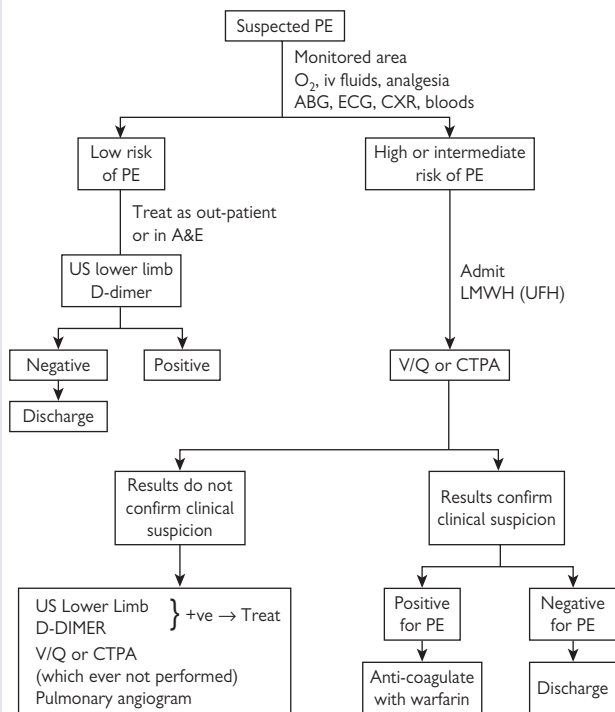



Fig. 17.7 Proposed pathway for investigation of patients with suspected PE. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd ed. Oxford: Oxford University Press.

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Pulmonary embolism: management

1. Stabilize the patient

- Unless an alternative diagnosis is made, the patient should be treated as for a pulmonary embolus until this can be excluded.
- Monitor cardiac rhythm, pulse, BP, and respiration rate every 15 minutes with continuous pulse oximetry and cardiac monitor. Ensure full resuscitation facilities are available.
- Obtain venous access and start IV fluids (crystalloid or colloid).
- Give maximal inspired oxygen via face mask to correct hypoxia. Mechanical ventilation may be necessary if the patient is tiring (beware of cardiovascular collapse when sedation is given for endotracheal intubation).
- Give LMWH or UFH to all patients with high or intermediate risk of PE until diagnosis is confirmed. Meta-analysis of multiple trials has shown LMWH to be superior to UFH, with a reduction in mortality and bleeding complications. For doses consult local formulary.
- If there is evidence of haemodynamic instability (systemic hypotension, features of right heart failure) or cardiac arrest, patients may benefit from thrombolysis with rt-PA or SK (same doses as used for treatment of STEMI (see  STEMI: reperfusion therapy (thrombolysis), p. 264).

2. Analgesia

- Patients may respond to oral non-steroidal anti-inflammatory drugs (NSAIDs).
- Opiate analgesia should be used with caution. The vasodilatation caused by these drugs may precipitate or worsen hypotension. Give small doses (1–2 mg diamorphine IV) slowly. Hypotension should respond to IV colloid.
- Avoid IM injections (anticoagulation and possible thrombolysis).

3. Investigations with view to a definite diagnosis

See previous section.

4. Anticoagulate

- Patients with a positive diagnosis must undergo anticoagulation with warfarin. There should be period of overlap with LMWH/UFH until INR values are therapeutic. Target INR is 2–3 for most cases.
- Standard duration of anticoagulation is:
 - 4–6 weeks for temporary risk factor
 - 3 months first idiopathic cases
 - at least 6 months for other cases
 - with recurrent events and underlying predisposition to thromboembolic events (e.g. antiphospholipid antibody syndrome), lifelong anticoagulation may be needed (as well as higher target INR>3).

Dosage of thrombolytic agents for pulmonary embolus

Alteplase (rt-PA)	100 mg over 2 h or 0.6 mg/kg over 15 min (maximum of 50 mg) followed by heparin.
Streptokinase	250 000 U over 30 min followed by 100 000 U/h infusion for 24 h

NB: contraindications for thrombolysis are identical to ones for STEMI (see [☞ STEMI: reperfusion therapy \(thrombolysis\)](#), p. 264).

Cardiac arrest (also see [☞ Adult advanced life support](#), p. 712)

- Massive PE may present as cardiac arrest with electromechanical dissociation (EMD). Exclude the other causes of EMD (see [☞ Universal treatment algorithm](#), p. 716).
- Chest compressions may help break up the thrombus and allow it to progress more distally, thereby restoring some cardiac output.
- If clinical suspicion of PE is high and there is no absolute contraindication to thrombolysis, give rt-PA (similar in dose to STEMI with a maximum of 50 mg (see [☞ STEMI: reperfusion therapy \(thrombolysis\)](#), p. 264) followed by heparin).
- If cardiac output returns, consider pulmonary angiography or inserting a PA catheter to try to mechanically disrupt the embolus.

Hypotension

The acute increase in pulmonary vascular resistance results in right ventricular dilatation and pressure overload, which mechanically impairs LV filling and function. Patients require a higher than normal right-sided filling pressure, but may be worsened by fluid overload.

- Insert an internal jugular sheath prior to anticoagulation. This can be used for access, later if necessary.
- If hypotensive, give colloid (e.g. 500 mL Haemacell[®] stat).
- If hypotension persists, invasive monitoring and/or inotropic support is required. The JVP is a poor indicator of the left-sided filling pressures in such cases. Adrenaline is the inotrope of choice.
- Femoro-femoral cardiopulmonary bypass may be used to support the circulation until thrombolysis or surgical embolectomy can be performed.
- Pulmonary angiography in a hypotensive patient is hazardous, as the contrast may cause systemic vasodilatation and cardiovascular collapse.

Pulmonary embolectomy

- In patients who have contraindications to thrombolysis and are in shock requiring inotropic support, there may be a role for embolectomy if appropriate skills are on site.
- This can be performed percutaneously in the catheterization laboratory, using a number of devices, or surgically on cardiopulmonary bypass.
- Percutaneous procedures may be combined with peripheral or central thrombolysis.
- Seek specialist advice early. The best results are obtained before onset of cardiogenic shock.

- Radiological confirmation of the extent and site of embolism is preferable before thoracotomy.
- Mortality is ~25–30%.

Inferior vena cava (IVC) filter

- Infrequently used, as there is little to suggest improved short- or long-term mortality.
- Filters are positioned percutaneously and, if possible, patients must remain anticoagulated to prevent further thrombus formation.
- Most are positioned infra-renally (bird's nest filter), but can also be supra-renal (Greenfield filter).
- Indications for IVC filter use include:
 - anticoagulation contraindicated: e.g. active bleeding, heparin-induced thrombocytopenia, planned intensive chemotherapy
 - anticoagulation failure despite adequate therapy
 - prophylaxis in high-risk patients: e.g. progressive venous thrombosis, severe pulmonary hypertension.

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Fat embolism

Commonly seen in patients with major trauma. There is embolization of fat and micro-aggregates of platelets, red blood cells, and fibrin in the systemic and pulmonary circulation. Pulmonary damage may result directly from the emboli (infarction) or by a chemical pneumonitis and ARDS.

Clinical features

- There may be a history of fractures followed (24–48 h later) by breathlessness, cough, haemoptysis, confusion, and rash.
- Examination reveals fever (38–39°C), widespread petechial rash (25–50%), cyanosis, and tachypnoea. There may be scattered crepitations in the chest, though examination may be normal. Changes in mental state may be the first sign, with confusion, drowsiness, seizures, and coma. Examine the eyes for conjunctival and retinal haemorrhages; occasionally, fat globules may be seen in the retinal vessels. Severe fat embolism may present as shock.

Investigations

- | | |
|--------------------|--|
| • ABG | • Hypoxia and a respiratory alkalosis (with low $P_a\text{CO}_2$) as for thromboembolic PE |
| • FBC | • Thrombocytopenia, acute intravascular haemolysis |
| • Coagulation | • Disseminated intravascular coagulation |
| • U&Es and glucose | • Renal failure, hypoglycaemia |
| • Ca^{2+} | • May be low |
| • Urine | • Microscopy for fat and dipstick for haemoglobin |
| • ECG | • Usually non-specific (sinus tachycardia; occasionally signs of right heart strain) |
| • CXR | • Usually lags behind the clinical course. There may be patchy, bilateral, air space opacification. Effusions are rare |
| • CT head | • Consider if there is a possibility of head injury with expanding subdural or epidural bleed |

Differential diagnosis

- Pulmonary thromboembolism, other causes of ARDS, septic shock, hypovolaemia, cardiac or pulmonary contusion, head injury, aspiration pneumonia, transfusion reaction.

Management

- Treat respiratory failure. Give oxygen (maximal via face mask; CPAP and mechanical ventilation if necessary).
- Ensure adequate circulating volume and cardiac output. Central venous pressure (CVP) is not a good guide to left-sided filling pressures, and a PA catheter (Swan–Ganz) should be used to guide fluid replacement. Try to keep PCWP at 12–15 mmHg and give diuretics if necessary. Use inotropes to support circulation as required.


- Aspirin, heparin and dextran 40 (500 mL over 4–6 h) are of some benefit in the acute stages, but may exacerbate bleeding from sites of trauma.
- High-dose steroids (methylprednisolone 30 mg/kg q8 h for 3 doses) have been shown to improve hypoxaemia,¹ but steroids are probably most effective if given prophylactically.

¹ Lindeque B, Schoeman H, Dommissie G, Boeyens MC, Vlok AL (1987). Fat embolism and the fat embolism syndrome. *J Bone Joint Surg* **69**: 128–31.

Hypertensive emergencies

Hypertensive crisis

Hypertensive crisis is defined as a severe elevation in blood pressure (systolic blood pressure (SBP) >200 mmHg, diastolic blood pressure (DBP) >120 mmHg). The rate of change in BP is important. A rapid rise is poorly tolerated and leads to end-organ damage, whereas a gradual rise in a patient with existent poor BP control is tolerated better. Hypertensive crisis are classified as:

1. **hypertensive emergency**, where a high BP is complicated by acute target organ dysfunction (see  Hypertensive emergencies, p. 754) and includes:

- *hypertensive emergency with retinopathy* where there is marked elevation in BP (classically DBP >40 mmHg) with retinal haemorrhages and exudates (previously called accelerated hypertension), and
- *hypertensive emergency with papilloedema* with a similarly high BP and papilloedema (previously called malignant hypertension).

2. **hypertensive urgency**, where there is a similar rise in BP, but without target organ damage.

Conditions that present as hypertensive emergency



- Essential hypertension
- Renovascular hypertension: atheroma, fibromuscular dysplasia, acute renal occlusion
- Renal parenchymal disease: acute glomerulonephritis, vasculitis, scleroderma.
- Endocrine disorders: pheochromocytoma, Cushing's syndrome, primary hyperaldosteronism, thyrotoxicosis, hyperparathyroidism, acromegaly, adrenal carcinoma
- Eclampsia and pre-eclampsia
- Vasculitis
- Drugs: cocaine, amphetamines, monoamine oxidase inhibitor (MAOI) interactions, ciclosporin, β -blocker, and clonidine withdrawal
- Autonomic hyperactivity in the presence of spinal cord injury
- Coarctation of the aorta

Presentation

- Occasionally there are minimal non-specific symptoms such as mild headache and nose bleed.
- A small group of patients present with symptoms resulting from BP-induced microvascular damage:
 - neurological symptoms: severe headache, nausea, vomiting, visual loss, focal neurological deficits, fits, confusion, intracerebral haemorrhage, coma (see later)
 - chest pain (hypertensive heart disease, MI, or aortic dissection) and congestive cardiac failure
 - symptoms of renal failure: renal impairment may be chronic (secondary to longstanding hypertension) or acute (from the necrotizing vasculitis of malignant hypertension).

- Patients may present with hypertension as one manifestation of an underlying 'disease' (renovascular hypertension, chronic renal failure, CREST syndrome (calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia), pheochromocytoma, pregnancy).
- Examination should be directed at looking for evidence of end-organ damage, even if the patient is asymptomatic (heart failure, retinopathy, papilloedema, focal neurology).

Hypertensive emergencies

- Hypertensive emergency with retinopathy/papilloedema
- Hypertensive encephalopathy
- Hypertension-induced intracranial haemorrhage/stroke
- Hypertension with cardiovascular complications:
 - Aortic dissection (see  Aortic dissection: assessment, p. 766)
 - MI
 - Pulmonary oedema (see  Acute pulmonary oedema: assessment, p. 724)
- Pheochromocytoma
- Pregnancy-associated hypertensive complications:
 - eclampsia and pre-eclampsia
 - Acute renal insufficiency
- Hypertensive emergency secondary to acute withdrawal syndromes (e.g. β -blockers, centrally acting antihypertensives)

Hypertensive emergencies: management

Priorities in management are:

1. confirm the diagnosis and assess the severity
2. identify those patients needing specific emergency treatment
3. plan long-term treatment.

Diagnosis and severity

- Ask about previous BP recordings, previous and current treatment, sympathomimetics, antidepressants, non-prescription drugs, recreational drugs.
- Check the blood pressure yourself, in both arms, after a period of rest and if possible on standing. Monitor the patient's blood pressure regularly while they are in the emergency department.
- Examine carefully for clinical evidence of cardiac enlargement or heart failure, peripheral pulses, renal masses, or focal neurological deficit. Always examine the fundi—dilate if necessary.

Investigations All patients should have:

-
- | | |
|----------------------|---|
| • FBC | • Microangiopathic haemolytic anaemia with malignant hypertension |
| • U&E | • Renal impairment and/or $\uparrow K^+$ (diffuse intrarenal ischaemia and 2° hyperaldosteronism) |
| • Coagulation screen | • Disseminated intravascular coagulation (DIC) with malignant hypertension |
| • CXR | • Cardiac enlargement; aortic contour (dissection?); pulmonary oedema |
| • Urinalysis | • Protein and red cells \pm casts |
-

Other investigations depending on clinical picture and possible aetiology include:

-
- | | |
|-------------------------|--|
| • 24-h urine collection | • Creatinine clearance |
| | • Free catecholamines, metanephrines or vanillyl mandelic acid (VMA) |
| • ECHO | • LVH, aortic dissection |
| • Renal USS and Doppler | • Size of kidneys and renal artery stenosis |
| • MR renal angiogram | • Renal artery stenosis |
| • CT/MR brain | • Intracranial bleed |
| • Drug screen | • Cocaine, amphetamine, others |
-

Indications for admission

- Diastolic blood pressure persistently ≥ 120 mmHg
- Retinal haemorrhages, exudates, or papilloedema
- Renal impairment

Voltage criteria for LVH

- Tallest R (V_4 – V_6) + deepest S (V_1 – V_3) >40 mm
- Tallest R (V_4 – V_6) >27 mm
- Deepest S (V_1 – V_3) >30 mm
- R in aVL >13 mm
- R in aVF >20 mm
- QRS complex >0.08 s (2 small squares)
- Abnormal ST depression or T inversion in V_4 – V_6



Treatment principles

- *Rapid reduction in BP is unnecessary, must be avoided, and can be very dangerous.* This can result in cerebral and cardiac hypoperfusion (an abrupt change of >25% in BP will exceed cerebral BP autoregulation).
- Initial BP reduction of 25% should be achieved over 1–4 hours, with a less rapid reduction over 24 hours to a DBP 100 mmHg.
- The only two situations where BP must be lowered rapidly are in the context of aortic dissection and MI.

Treatment

- The majority of patients who are alert and otherwise well may be treated with oral therapy to lower BP gradually.
- First-line treatment should be with a β -blocker (unless contraindicated), with a thiazide diuretic, or a low-dose calcium channel antagonist.
- Urgent invasive monitoring (arterial line) prior to drug therapy is indicated for patients with:
 - evidence of hypertensive encephalopathy
 - complications of hypertension (e.g. aortic dissection, acute pulmonary oedema, or renal failure)
 - treatment of underlying condition (e.g. glomerulonephritis, pheochromocytoma, CREST crisis)
 - persistent diastolic BP \geq 140 mmHg
 - eclampsia.
- Sublingual nifedipine must be avoided.

Conditions requiring specific treatment

- Accelerated and malignant hypertension (see  Hypertensive emergency with retinopathy (accelerated and malignant hypertension), p. 762)
- Hypertensive encephalopathy (see  Hypertensive encephalopathy, p. 764)
- Eclampsia
- Pheochromocytoma
- Hypertensive patients undergoing anaesthesia

Long-term management

- Investigate as appropriate for an underlying causes.
- Select a treatment regime that is tolerated and effective. Tell the patient why long-term therapy is important.
- Try to reduce all cardiovascular risk factors by advising the patient to stop smoking, appropriate dietary advice (cholesterol), and aim for optimal diabetic control.
- Monitor long-term control and look for end-organ damage (regular fundoscopy, ECG, U&Es). Even poor control is better than no control.

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Drugs for hypertensive emergencies

See Tables 17.3 (IV therapy) and 17.4 (oral therapy).

Table 17.3 Drugs for the treatment of hypertensive emergencies: IV therapy

Drug	Dosage	Onset of action	Comments
Labetalol	20–80 mg IV bolus q10min 20–200 mg/min by IV infusion increasing every 15 minutes	2–5 minutes	Drug of choice in suspected phaeochromocytoma or aortic dissection (see 📖 STEMI: additional measures, p. 270). Avoid if there is LV failure (LVF). May be continued orally (see below)
Nitroprusside	0.25–8 mcg/kg/min IV infusion (see 📖 Pericardial aspiration, p. 814–6)	Seconds	Drug of choice in LVF and/or encephalopathy
GTN	1–10 mg/hr IV infusion	2–5 minutes	Mainly venodilatation. Useful in patients with LVF or angina
Hydralazine	5–10 mg IV over 20 min 50–300 mcg/min IV infusion	10–15 minutes	May provoke angina
Esmolol HCl	500 mcg/kg IV loading dose 50–200 mcg/kg/min IV infusion	Seconds	Short acting β -blocker also used for SVTs
Phentolamine	2–5 mg IV over 2–5 min prn	Seconds	

NB: it is dangerous to reduce the blood pressure quickly. Aim to reduce the diastolic BP to 100–110 mmHg within 2–4 h. Unless there are good reasons to commence IV therapy, always use oral medicines.

Table 17.4 Drugs for the treatment of hypertensive emergencies: oral therapy

Drug	Dosage	Onset of action	Comment
Atenolol	50–100 mg PO od	30–60 minutes	There are numerous alternative β -blockers—see <i>British National Formulary</i> (BNF)
Nifedipine	10–20 mg PO q8h (q12h if slow release)	15–20 minutes	Avoid sublingual as the fall in BP is very rapid
Labetalol	100–400 mg PO q12h	30–60 minutes	Use if phaeochromocytoma suspected. Safe in pregnancy
Hydralazine	25–50 mg PO q8h	20–40 minutes	Safe in pregnancy
Minoxidil	5–10 mg PO od	30–60 minutes	May cause marked salt and water retention. Combine with a loop diuretic (e.g. furosemide 40–240 mg daily)
Clonidine	0.2 mg PO followed by 0.1 mg hourly 0.8 mg total for urgent therapy, or 0.05–0.1 mg PO q8 h increasing every 2 days	30–60 minutes	Sedation common. Do not stop abruptly as there is a high incidence of rebound hypertensive crisis


NB: aim to reduce diastolic BP to 100–110 mmHg in 2–4 h and normalize BP in 2–3 days.

Hypertensive emergency with retinopathy (accelerated and malignant hypertension)

This is part of a continuum of disorders characterized by hypertension (diastolic BP often >120 mmHg) and acute microvascular damage (seen best in the retina but present in all organs). It may be difficult to decide whether the damage in some vascular beds is the cause or effect of hypertension (e.g. an acute glomerulonephritis).

- Accelerated hypertension (grade 3 retinopathy) may progress to malignant hypertension, with widespread necrotizing vasculitis of the arterioles (and papilloedema).
- Presentation is commonly with headache or visual loss and varying degrees of confusion. More severe cases present with renal failure, heart failure, microangiopathic haemolytic anaemia, and DIC.

Management

- Transfer the patient to medical HDU/ITU.
- Insert an arterial line and consider a central venous line if there is evidence of necrotizing vasculitis and DIC. Catheterize the bladder.
- Monitor neurological state, ECG, fluid balance.
- Aim to lower the DBP to 100 mmHg or by 15–20 mmHg, whichever is higher, over the first 24 hours.
- Those with early features may be treated successfully with oral therapy (β -blockers, calcium-channel blockers—see  Table 17.4, p. 761)
- Patients with late symptoms or who deteriorate should be given parenteral therapy aiming for more rapid lowering of BP.
 - If there is evidence of pulmonary oedema or encephalopathy give furosemide 40–80 mg IV.
 - If there is no LVF, give a bolus of labetalol followed by an infusion. For patients with LVF, nitroprusside or hydralazine are preferable.
- Consult the renal team for patients with acute renal failure or evidence of acute glomerulonephritis (>2+ proteinuria, red cell casts). Dopamine should be avoided as it may worsen hypertension.
- Consider giving an ACE-I. High circulating renin levels may not allow control of hypertension, which in turn causes progressive renal failure. ACE-Is will block this vicious circle. There may be marked first-dose hypotension, so start cautiously.
- Haemolysis and DIC should recover with control of BP.

Hypertension in the context of acute stroke/intracranial bleed

- Stroke/bleed may be the result of hypertension, or vice versa.
- In the acute setting there is impaired autoregulation of cerebral blood flow and autonomic function. Small changes in systemic BP may result in catastrophic falls in cerebral blood flow.
- SBP should not be treated unless DBP > 130 mmHg and/or severe cerebral oedema (with clinical manifestations) is present.
- In most cases, BP tends to settle over 24–36 hours. If treatment is indicated, the above BP-reduction principles must be adhered to and a combination of nitroprusside, labetalol and calcium-channel blockers can be used.
- Centrally acting agents must be avoided as they cause sedation.
- In patients with subarachnoid haemorrhage (SAH), a cerebroselective calcium-channel blocker, such as nimodipine, is used to decrease cerebral vasospasm.
- Systemic BP must also be treated, if it qualifies the above principles and/or if it remains elevated after 24 hours. There is no evidence that this reduces further events in the acute phase.

Hypertensive retinopathy

Grade 1	Tortuous retinal arteries, silver wiring
Grade 2	AV nipping
Grade 3	Flame-shaped haemorrhages and cotton wool exudates
Grade 4	Papilloedema

Hypertensive encephalopathy

- Hypertensive encephalopathy is caused by cerebral oedema 2° to loss of cerebral autoregulatory function.
- Usually, there is gradual onset and it may occur in previously normotensive patients at blood pressures as low as 150/100 mmHg. It is rare in patients with chronic hypertension, and pressures are also much higher.

Symptoms

- Headache, nausea and vomiting, confusion, grade III and IV hypertensive retinopathy
- Late features consist of focal neurological signs, fits, and coma

Diagnosis

- Hypertensive encephalopathy is a diagnosis of exclusion, and other differential diagnosis must be ruled out (e.g. stroke, encephalitis, tumours, bleeding, vasculitis).
- History is helpful, particularly of previous seizures, SAH usually being sudden in onset and strokes being associated with focal neurological deficit.
- Always exclude hypoglycaemia.
- Starting hypotensive treatment for hypertension associated with a stroke can cause extension of the stroke.
- *An urgent MRI or CT brain must be obtained to rule out some of the differential diagnoses.*

Management


- The primary principle of blood pressure control is to reduce DBP by 25% or reduce DBP to 100 mmHg, whichever is higher, over a period of 1–2 hours.
- Transfer the patient to ITU for invasive monitoring (see previous section).
- Monitor neurological state, ECG, fluid balance.
- Correct electrolyte abnormalities (K^+ , Mg^{2+} , Ca^{2+}).
- Give furosemide 40–80 mg IV.
- Nitroprusside is the first-line agent, as it is easy to control BP changes, despite its tendency to increase cerebral blood flow.
- Labetalol and calcium-channel blockers are second-line agents and should be added in if necessary.
- It is vital to avoid agents with potential sedative action such as β -blockers, clonidine, and methyldopa.
- In selected patients who are stable and present at the very early stages, oral therapy with a combination of β -blockers and calcium-channel blockers may be sufficient.

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Aortic dissection: assessment

Aortic dissection is a surgical/medical emergency and, untreated, has a >90% one-year mortality. Dissection begins with formation of a tear in the intima and the force of the blood cleaves the media longitudinally to various lengths. Predisposing factors are summarized on the next page.

Classification

There are three classifications as illustrated in Fig. 17.8  Aortic dissection: investigations, p. 769—DeBakey, Stanford, and descriptive. Dissections involving the ascending and/or aortic arch are surgical emergencies and those that are exclusive to the descending aorta are treated medically.

Presentation

Chest pain: Classically abrupt onset, very severe in nature and most commonly anterior chest pain radiating to the interscapular region. Usually tearing in nature and, unlike the pain of MI, most severe at its onset. Pain felt maximally in the anterior chest is associated with ascending aortic dissection, whereas interscapular pain suggests dissection of the descending aorta. Patients often use adjectives such as ‘tearing’, ‘ripping’, ‘sharp’ and ‘stabbing’ to describe the pain.

Sudden death or shock: Usually due to aortic rupture or cardiac tamponade.

Congestive cardiac failure: Due to acute aortic incompetence and/or MI.

- Patients may also present with symptoms and signs of occlusion of one of the branches of the aorta. Examples include:
 - stroke or acute limb ischaemia—due to compression or dissection
 - paraplegia with sensory deficits—spinal artery occlusion
 - MI—usually the right coronary artery
 - renal failure and renovascular hypertension
 - abdominal pain—coeliac axis or mesenteric artery occlusion.
- Aortic dissection may be painless.
- Ask specifically about history of hypertension, previous heart murmurs or aortic valve disease, and previous CXRs that may be useful for comparison.

Examination

- This may be normal.
- Most patients are hypertensive on presentation. Hypotension is more common in dissections of the ascending aorta (20–25%) and may be due to blood loss, acute aortic incompetence (which may be accompanied by heart failure), or tamponade (distended neck veins, tachycardia, pulsus paradoxus).
- Pseudohypotension may be seen if flow to either or both subclavian arteries is compromised. Look for unequal blood pressure in the arms and document the presence of peripheral pulses carefully. Absent or changing pulses suggests extension of the dissection.
- Auscultation may reveal aortic valve regurgitation and, occasionally, a pericardial friction rub. Descending aortic dissections may rupture or leak into the left pleural space, and the effusion results in dullness in the left base.

- Neurologic deficits may be due to carotid artery dissection or compression (hemiplegia) or spinal artery occlusion (paraplegia with sensory loss).

Conditions associated with aortic dissection

- | | |
|---------------------------------|--|
| • Hypertension | • Smoking, dyslipidaemia, cocaine/crack |
| • Connective tissue disorders | • Marfan syndrome ^a
• Ehlers–Danlos syndrome |
| • Hereditary vascular disorders | • Bicuspid aortic valve
• Coarctation |
| • Vascular inflammation | • Giant cell arteritis
• Takayasu arteritis
• Behçet's disease
• Syphilis |
| • Deceleration trauma | • Car accident
• Falls |
| • Chest trauma | |
| • Pregnancy | |
| • Iatrogenic | • Catheterization
• Cardiac surgery |

^aMarfan syndrome (arm span > height, pubis to sole > pubis to vertex, depressed sternum, scoliosis, high arched palate, upward lens dislocation, thoracic aortic dilation/aortic regurgitation, increased urinary hydroxyproline (some)).

Differential diagnosis

- The chest pain may be mistaken for acute MI and acute MI may complicate aortic dissection. Always look for other signs of dissection (see above), as thrombolysis will be fatal.
- Severe chest pain and collapse may also be due to pulmonary embolism, spontaneous pneumothorax, acute pancreatitis, and penetrating duodenal ulcer.
- Pulse deficits without backache should suggest other diagnoses: atherosclerotic peripheral vascular disease, arterial embolism, Takayasu arteritis, etc.
- Acute cardiac tamponade with chest pain is also seen in acute viral or idiopathic pericarditis, and acute MI with external rupture.

Aortic dissection: investigations

General

- **ECG** may be normal or non-specific (LVH, ST/T abnormalities). Look specifically for evidence of acute MI (inferior MI is seen if the dissection compromises the right coronary artery ostium).
- **CXR** may appear normal, but with hindsight is almost always abnormal. Look for widened upper mediastinum, haziness or enlargement of the aortic knuckle, irregular aortic contour, separation (>5 mm) of intimal calcium from outer aortic contour, displacement of the trachea to the right, enlarged cardiac silhouette (pericardial effusion), pleural effusion (usually on left). Compare with previous films if available.
- **Bloods:** Base FBC, U&E, cardiac enzyme as well as cross match. A novel monoclonal antibody assay to smooth muscle myosin heavy chains can accurately differentiate an acute dissection from a MI.

Diagnostic

- **Echocardiography:** *Transthoracic ECHO* may be useful in diagnosing aortic root dilatation, aortic regurgitation, and pericardial effusion/tamponade. *TOE* is the investigation of choice as it allows better evaluation of both the ascending aorta and descending aorta, may identify the origin of the intimal tear, allows evaluation of the origins of the coronary arteries in relation to the dissection flap, and provides information on aortic insufficiency. It is not good at imaging the distal ascending aorta and proximal arch.
- **MRI angiography** is the gold standard for diagnosing aortic dissection. It has all the positive features of TOE and, in particular, also provides accurate information on all segments of the ascending/arch/descending aorta, entry/exit sites, and branch vessels. Images can be displayed in multiple views as well as reconstructed in three dimensions. However, there are a number of disadvantages, including (1) the availability of service out of hours and cost; (2) the presence of metallic valves or pacemakers may preclude the patient from having an MRI; (3) monitoring of unstable patients in the scanner can be difficult and unsafe.
- **Spiral (helical) CT with contrast** allows three-dimensional display of all segments of the aorta and adjacent structures. True and false lumen are identified by differential contrast flow; the entry and exit site of the intimal flap can be seen, as well as pleural and pericardial fluid. However, it cannot demonstrate disruption of the aortic valve, which may be associated with ascending aortic dissection.
- **Angiography** using the femoral or axillary approach may demonstrate altered flow in the two lumens, aortic valve incompetence, and involvement of the branches and the site of the intimal tear. It is invasive and associated with a higher risk of complications in an already high-risk patient. It has largely been superseded by CT/MRI and TOE.

Selecting a diagnostic modality

- Confirm or refute a diagnosis of dissection.
- Is the dissection confined to the descending aorta or does it involve the ascending/arch?
- Identify the extent, sites of entry and exit, and presence and absence of thrombus.
- Aim to see whether there is aortic regurgitation, coronary involvement, or pericardial effusions.

Selecting a diagnostic modality

- Where available, TOE should be the first-line investigation. It is safe and can provide all the information necessary to take the patient to the operating theatre.
- If TOE is not available, or if it fails to provide the necessary information, a spiral contrast CT should be performed.
- MRI should generally be reserved for follow-up images.
- Angiography is rarely used, but is of value if other modalities have failed to provide a diagnosis, and/or extensive information is needed on branch vessels.

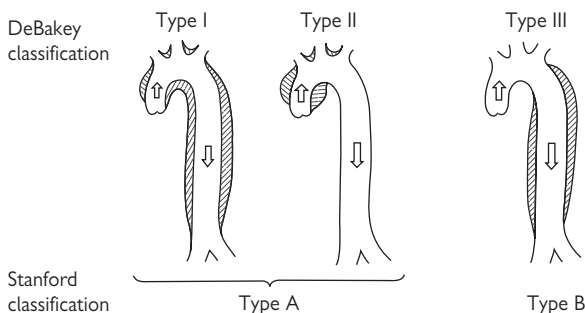



Fig. 17.8 Clarification of aortic dissection.

Aortic dissection: management

Stabilize the patient

- If the diagnosis is suspected, transfer the patient to an area where full resuscitation facilities are readily available.
- Secure *venous access* with large-bore cannulae (e.g. grey Venflon).
- *Take blood* for FBC, U&Es, and cross match (10 units).
- When the diagnosis is confirmed, or in cases with cardiovascular complications, *transfer to ITU*, insert an *arterial line* (radial unless the subclavian artery is compromised when a femoral line is preferred), *central venous line*, and *urinary catheter*.
- Immediate measures should be taken to correct blood pressure (see below).
- Give adequate analgesia (diamorphine 2.5–10 mg IV and metoclopramide 10 mg IV).

Plan the definitive treatment

This depends on the type of dissection (see Fig. 17.8  Aortic dissection: investigations, p. 769) and its effects on the patient. General principles are:

- patients with involvement of the ascending aorta should have *emergency surgical repair and BP control*
- patients with dissection limited to the descending aorta are managed initially medically, with aggressive BP control.

However, this may change in the near future, with encouraging data emerging from deployment of endovascular stent-grafts.

Indications and principles for surgery

- Involvement of the ascending aorta
- External rupture (haemopericardium, haemothorax, effusions)
- Arterial compromise (limb ischaemia, renal failure, stroke)
- Contraindications to medical therapy (AR, LVF)
- Progression (continued pain, expansion of haematoma on further imaging, loss of pulses, pericardial rub, or aortic insufficiency)

The aim of surgical therapy is to replace the ascending aorta, thereby preventing retrograde dissection and cardiac tamponade (the main cause of death). The aortic valve may need reconstruction and resuspension unless it is structurally abnormal (bicuspid or Marfan), where it is replaced.

Indications and principles for medical management


Medical therapy is the treatment of choice for:

- uncomplicated type B dissection
- stable isolated arch dissection
- chronic (>2 weeks' duration) stable type B dissection.

In all but those patients who are hypotensive, initial management is aimed at reducing systemic blood pressure and myocardial contractility. The goal is to stop spread of the intramural haematoma and to prevent rupture. The best guide is control of pain. Strict bed rest in a quiet room is essential.

Control blood pressure

Reduce systolic BP to 100–120 mmHg.

- Start on IV β -blocker (if no contraindications), aiming to reduce the heart rate to 60–70/min (see box,  p.772).
- Once this is achieved, if blood pressure remains high, add a vasodilator such as sodium nitroprusside (see box opposite). Vasodilators in the absence of β -blockade may increase myocardial contractility and the rate of rise of pressure (dP/dt). Theoretically, this may promote extension of the dissection.
- Further antihypertensive therapy may be necessary, and other conventional agents such as calcium-channel blockers, β -blockers, and ACE-Is can be used.
- In patients with aortic regurgitation and congestive cardiac failure, myocardial depressants should not be given. Aim to control BP with vasodilators only.

Hypotension may be due to haemorrhage or cardiac tamponade.

- Resuscitate with rapid intravenous volume (ideally colloid or blood, but crystalloid may be used also). A pulmonary artery wedge catheter (Swan–Ganz) should be used to monitor the wedge pressure and guide fluid replacement.
- If there are signs of aortic regurgitation or tamponade, arrange for an urgent ECHO and discuss with the surgeons.

Emerging indications and principles for interventional therapy

There are increasing reports and short case series demonstrating favourable outcome (prognostic as well as symptomatic) data on using endovascular stent-grafts in management of primarily type B and also, to a lesser extent, type A aortic dissections.

On the basis of the current evidence, endovascular stent-grafts should be considered to seal the entry to false lumen and to enlarge compressed true lumen in the following situations:

- unstable type B dissection
- malperfusion syndrome (proximal aortic stent-graft and/or distal fenestration/stenting of branch arteries)
- routine management of type B dissection (under evaluation).

Cardiac tamponade: If the patient is relatively stable, pericardiocentesis may precipitate haemodynamic collapse and should be avoided. The patient should be transferred to the operating theatre for direct repair as urgently as possible. In the context of tamponade and EMD or marked hypotension, pericardiocentesis is warranted.

Long-term treatment must involve strict BP control.

Prognosis

- The mortality for untreated aortic dissection is roughly 20–30% at 24 hours and 65–75% at 2 weeks.
- For dissections confined to the descending aorta, short-term survival is better (up to 80%) but ~30–50% will have progression of dissection despite aggressive medical therapy, and require surgery.
- Operative mortality is of the order of 10–25% and depends on the condition of the patient preoperatively. Postoperative 5-year actuarial survival of up to 75% may be expected.

Medical therapy of aortic dissection

β-blockade (aim for heart rate (HR) <60–70/min)

Labetalol	20–80 mg slow IV injection over 10 min then 20–200 mg/h IV, increasing every 15 min 100–400 mg PO q12h
Atenolol	5–10 mg slow IV injection then 50 mg PO after 15 min and at 12 h, then 100 mg PO daily
Propranolol	0.5 mg IV (test dose), then 1 mg every 2–5 min up to max 10 mg; repeat every 2–3 h 10–40 mg PO 3–4 times daily


When HR 60–70 /min, (or if β-blocker contraindicated), add

Nitroprusside	0.25–10 mcg/kg/min IV infusion
Hydralazine	5–10 mg IV over 20 minutes 50–300 mcg/min IV infusion 25–50 mg PO q8h
GTN	1–10 mg/h IV infusion
Amlodipine	5–10 mg PO od

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Acute pericarditis: assessment

Presentation

- Typically presents as central chest pain—often pleuritic—relieved by sitting forward and can be associated with breathlessness.
- Other symptoms (e.g. fever, cough, arthralgia, rash, faintness/dizziness secondary to pain/ \uparrow HR) may reflect the underlying disease.
- A pericardial friction rub is pathognomonic. This may be positional and transient and may be confused with the murmur of tricuspid regurgitation (TR) or MR.
- Venous pressure rises if an effusion develops. Look for signs of cardiac tamponade (see  Cardiac tamponade: presentation, p. 778).

Investigations

- ECG**
- May be normal in up to 10%.
 - ‘Saddle-shaped’ ST-segment elevation (concave upwards), with variable T inversion (usually late stages) and PR-segment depression (opposite to P-wave polarity). Minimal lead involvement to be considered typical includes I, II, aVL, aVF and V₃–V₆.
 - ST-segment is always depressed in aVR, frequently depressed or isoelectric in V₁, and sometimes depressed in V₂.
 - May be difficult to distinguish from acute MI. Features suggesting pericarditis are:
 - concave ST elevation (vs. convex)
 - all leads involved (vs. a territory e.g. inferior)
 - failure of usual ST evolution and no Q waves
 - no AV block, BBB, or QT prolongation.
 - Early repolarization (a normal variant) may be mistaken for pericarditis. In the former, ST elevation occurs in precordial and, rarely, in V₆ or the limb leads, and is unlikely to show ST depression in V₁ or PR segment depression.
 - Usually not helpful in diagnosing pericarditis post-MI.
 - The voltage drops as an effusion develops, and in tamponade there is electrical alternans, best seen in QRS complexes.
-
- ECHO**
- May demonstrate a pericardial collection.
 - Useful to monitor LV function in case of deterioration due to associated myopericarditis.
 - We recommend every patient has an ECHO prior to discharge to assess LV function.

Other investigations depend on the suspected aetiology.

All patients should have:

- FBC and biochemical profile
- ESR and CRP (levels rise proportionate to intensity of disease)
- serial cardiac enzymes (CK, CK-MB, troponin)—elevations indicate subpericardial myocarditis
- CXR (heart size, pulmonary oedema, infection).

And, where appropriate:


- viral titres (acute + 2 weeks later)—and obtain virology opinion
- blood cultures
- autoantibody screen (rheumatoid factor (RF), ANA, anti-DNA, complement levels)
- thyroid function tests (TFTs)
- fungal precipitins (if immunosuppressed), ↑Mantoux test
- sputum culture and cytology
- diagnostic pericardial tap (culture, cytology).

Causes of acute pericarditis

- Idiopathic
- Infection (viral, bacterial, tuberculosis (TB), and fungal)
- Acute MI
- Dressler's syndrome, post-cardiotomy syndrome
- Malignancy (e.g. breast, bronchus, lymphoma)
- Uraemia
- Autoimmune disease (e.g. SLE, rheumatoid arthritis (RA), Wegner's, scleroderma, polyarteritis nodosa (PAN))
- Granulomatous diseases (e.g. sarcoid)
- Hypothyroidism
- Drugs (hydralazine, procainamide, isoniazid)
- Trauma (chest trauma, iatrogenic)
- Radiotherapy

Acute pericarditis: management

General measures

- **Admit?** This depends on the clinical picture. We recommend admission of most patients for observation for complications, especially effusions, tamponade, and myocarditis. Patients should be discharged when pain free.
- **Bed rest**
- **Analgesia:** NSAIDs are the mainstay. Ibuprofen is well tolerated and increases coronary flow (200–800 mg qds). Aspirin is an alternative (600 mg qds PO). Indometacin should be avoided in adults as it reduces coronary flow and has marked side-effects. Use a proton pump inhibitor (PPI) (lansoprazole 30 mg od) to minimize gastrointestinal (GI) side-effects. Opioid analgesia may be required. Colchicine used as monotherapy or in addition to NSAIDs may help settle pain acutely and prevent recurrence.
- **Steroids:** These may be used if the pain does not settle within 48 hours (e.g. prednisolone 40–60 mg PO od for up to 2 weeks, tapering down when pain settles). Use in conjunction with NSAID and taper steroids first before stopping NSAID. It is also of value if pericarditis is 2° to autoimmune disorders.
- **Colchicine:** Anecdotal evidence suggests that either used as monotherapy or in conjunction with NSAIDs it may help to settle pain acutely and prevent relapses (1 mg/day divided doses). Stop if patient develops diarrhoea or nausea (1 mg stat, 500 mcg q6h for 48h).
- **Pericardiocentesis:** This should be considered for significant effusion or if there are signs of tamponade (see  Cardiac tamponade: presentation, p. 778).
- **Antibiotics:** These should be given only if bacterial infection is suspected.
- **Oral anticoagulants** should be discontinued (risk of haemo-pericardium). Patient should be given IV UFH, which is easier to reverse (IV protamine) if complications arise.

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Cardiac tamponade: presentation

Cardiac tamponade occurs when a pericardial effusion causes haemodynamically significant cardiac compression. The presentation depends on the speed with which fluid accumulates within the pericardium. Acute tamponade may occur with 100–200 mL in a relatively restricted pericardial sac. Chronic pericardial collections may contain up to 1000 mL of fluid without clinical tamponade.

Causes

Acute tamponade

- Cardiac trauma
- Iatrogenic:
 - post-cardiac surgery
 - post-cardiac catheterization
 - post-pacing/EP study
- Aortic dissection
- Spontaneous bleed:
 - anticoagulation
 - uraemia
 - thrombocytopenia
- Cardiac rupture post-MI

'Subacute' tamponade

- Malignant disease
- Idiopathic pericarditis
- Uraemia
- Infections
 - Bacterial:
 - TB
- Radiation
- Hypothyroidism
- Post pericardotomy
- SLE

EP = electrophysiology.

Presentation

- Patients commonly present either with cardiac arrest (commonly electrical mechanical dissociation) or hypotension, confusion, stupor, and shock.
- Patients who develop cardiac tamponade slowly are usually acutely unwell, but not in extremis. Their main symptoms include:
 - breathlessness, leading to air hunger at rest
 - there may be a preceding history of chest discomfort
 - symptoms resulting from compression of adjacent structures by a large effusion (i.e. dysphagia, cough, hoarseness, or hiccough)
 - there may be symptoms due to the underlying cause
 - insidious development may present with complications of tamponade, including renal failure, liver and/or mesenteric ischaemia, and abdominal plethora.

Important physical signs

- Most physical findings are non-specific. They include:
 - tachycardia (except in hypothyroidism and uraemia)
 - hypotension (\pm shock) with postural hypotension
 - raised JVP (often >10 cm) with a prominent systolic x descent and absent diastolic y descent. If the JVP is visible and either remains static or rises with inspiration, it indicates concomitant pericardial constriction (Kussmaul's sign).

- Auscultation may reveal diminished heart sounds. Pericardial rub may be present and suggests a small pericardial collection.
- Look for pulsus paradoxus (a decrease in the palpable pulse and systolic BP of >10 mmHg on inspiration). This may be so marked that the pulse and Korotkoff sounds may be completely lost during inspiration. This can be measured using a BP cuff¹ or arterial catheter if *in situ* already. Other conditions that can cause a pulsus paradoxus include: acute hypotension, obstructive airways disease, and pulmonary embolus.
- Other physical signs include cool extremities (ears, nose) tachypnoea, hepatomegaly, and signs of the underlying cause for the pericardial effusion.

Causes of hypotension with a raised JVP

- Cardiac tamponade
- Constrictive pericarditis
- Restrictive pericarditis
- Severe biventricular failure
- Right ventricular infarction
- Pulmonary embolism
- Tension pneumothorax
- Acute severe asthma
- Malignant SVC obstruction and sepsis (e.g. lymphoma).

1 Teaching point: to establish the presence of pulsus paradoxus, non-invasively inflate a BP cuff to 15 mmHg above highest systolic pressure. Deflate the cuff gradually until the first beats are heard and hold the pressure at that level, concentrating on disappearance and reappearance of sounds with respiration (bump–bump, silence–silence, bump–bump, where noise reflects expiration). Continue to deflate slowly, paying attention to the same pattern until all beats are audible. The difference between the initial and final pressure should be greater than 10 mmHg.

Cardiac tamponade: management

Tamponade should be suspected in patients with hypotension, elevated venous pressure, falling BP, ↑HR, and ↑RR (respiratory rate; with clear chest), and pulsus paradoxus, especially if predisposing factors are present.

Investigations

- **Chest X-ray:** The heart size may be normal (e.g. in acute haemopericardium following cardiac trauma). With slower accumulation of pericardial fluid (>250 mL), the cardiac silhouette will enlarge with a globular appearance. The size of the effusion is unrelated to its haemodynamic significance. Look for signs of pulmonary oedema.
- **ECG:** Usually shows a sinus tachycardia, with low-voltage complexes and variable ST-segment changes. With large effusions, 'electrical alternans' may be present with beat-to-beat variation in the QRS morphology resulting from the movement of the heart within the pericardial effusion.
- **Echocardiography** confirms the presence of a pericardial effusion. The diagnosis of tamponade is a clinical one. ECHO signs highly suggestive of tamponade include: (1) chamber collapse during diastole (RA, RV, RV outflow tract); (2) marked variation in transvalvular flow; (3) dilated IVC with little or no diameter change on respiration.
- If available, examine the central venous pressure trace for the characteristic exaggerated x descent and absent y descent.

Management

Following confirmation of the diagnosis:

- while preparing for drainage of the pericardial fluid, the patient's circulation may temporarily be supported by loading with IV colloid (500–1000 mL stat) and starting inotropes (i.e. adrenaline)
- in patients with an adequate blood pressure, cautious systemic vasodilatation with hydralazine or nitroprusside in conjunction with volume loading, may increase forward cardiac output. This is not to be recommended routinely, as it may cause acute deterioration
- The effusion should be urgently drained (see [Pericardial aspiration](#), p. 814–6 for pericardiocentesis) guided by ECHO or fluoroscopy. *In the event of circulatory collapse, drainage must happen immediately without imaging.*
- surgical drainage is indicated if the effusion is secondary to trauma.
- avoid intubation and positive pressure ventilation as this reduces cardiac output.
- in patients with cardiac arrest, chest compression has little or no value, as there is no room for additional filling.
- uraemic patients will also need dialysis.
- the cause of the effusion should be established (see [Acute pericarditis: assessment](#), p. 774). Pericardial fluid should be sent for cytology, microbiology including TB, and, if appropriate Hb, glucose, and amylase.

Further management is of the underlying cause.

Special cases

- **Recurrent pericardial effusion:** In some cases, pericardial effusion recurs. This requires either a change in the treatment of the underlying cause or a formal surgical drainage procedure such as a surgical pericardial window or pericardiectomy.
- **Low-pressure tamponade:** Seen in the setting of dehydration. The JVP is not raised, right atrial pressure is normal, and tamponade occurs even with small volumes of pericardial fluid.
 - The patient may respond well to IV fluids.
 - If there is a significant pericardial collection, this should be drained.

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Practical procedures

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Arterial blood sampling

An arterial blood sample is used to measure the arterial oxygen tension (PaO_2), carbon dioxide tension (PaCO_2), pH and bicarbonate/base excess levels, and haemoglobin (Hb) saturation (SaO_2).

Familiarize yourself with the location and the use of the blood gas machine. Arterial blood is obtained either by percutaneous needle puncture or from an indwelling arterial line.

Radial artery

The radial artery is more accessible and more comfortable for the patient; it is best palpated between the bony head of the distal radius and the tendon of the flexor carpi radialis with the wrist dorsiflexed. The Allen test is used to identify impaired collateral circulation in the hand (a contraindication to radial artery puncture): the patient's hand is held high, with the fist clenched and both the radial and ulnar arteries compressed. The hand is lowered, the fist is opened, and the pressure from the ulnar artery is released. Colour should return to the hand within 5 seconds.

Brachial artery

The brachial artery is best palpated medial to the biceps tendon in the antecubital fossa, with the arm extended and the palm facing up. The needle is inserted just above the elbow crease.

Femoral artery

The femoral artery is best palpated just below the midpoint of the inguinal ligament, with the leg extended. The needle is inserted below the inguinal ligament at a 90 degree angle.

The chosen puncture site should be cleaned. Local anaesthetic should be infiltrated (not into the artery). Use one hand to palpate the artery and the other hand to advance the heparin-coated syringe and needle (22–25 gauge) at a 60–90 degree angle to the skin, with gentle aspiration. A flush of bright red blood indicates successful puncture. Remove about 2–3 mL of blood, withdraw the needle, and ask an assistant to apply pressure to the puncture site for 5–15 minutes. Air bubbles should be removed. The sample is placed on ice and analysed within 15 minutes (to reduce oxygen consumption by white blood cells (WBCs)).

Complications

These include persistent bleeding, bruising, injury to the blood vessel, and local thrombosis.

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Arterial line insertion: introduction


Indications

- Continuous monitoring of arterial blood pressure in critically ill patients with haemodynamic instability.
- Repeated arterial blood sampling.

Contraindications

- Coagulopathy
- Raynaud's phenomenon
- Thromboangiitis obliterans
- Advanced atherosclerosis
- End arteries such as the brachial artery should be avoided.

Initial measures

- Locate a palpable artery (e.g. radial or femoral).
- Assess ulnar blood flow using the Allen test, before inserting a radial line (see  Arterial blood sampling, p. 784).
- Position the hand in moderate dorsiflexion with the palm facing up (to bring the artery closer to the skin).
- The site should be cleaned with a sterile preparation solution and draped appropriately.
- Use sterile gloves.
- Use local anaesthetic (1% lidocaine) in a conscious patient.

Arterial line insertion: over-the-wire technique (see Fig. 18.1)

- Palpate the artery with the non-dominant hand (1–2 cm from the wrist between the bony head of the distal radius and the flexor carpi radialis tendon).
- The catheter and needle are advanced towards the artery at a 30–45° angle (Fig. 18.1(a)) until blood return is seen (Fig. 18.1(b)).
- The catheter and needle are then advanced through the vessel a few millimetres further (Fig. 18.1(c)).
- The needle is removed (Fig. 18.1(d)).
- The catheter is slowly withdrawn until pulsatile blood flow is seen (Fig. 18.1(e)).
- When pulsatile blood flow is seen, the wire is advanced into the vessel (Fig. 18.1(f)).
- The catheter is advanced further into the vessel *over the wire* (Fig. 18.1(g)).
- While placing pressure over the artery, the wire is removed (Fig. 18.1(h)) and the catheter is connected to a transduction system.
- Secure the catheter in place using suture or tape.
- Check perfusion to the hand after insertion of the arterial line and at frequent intervals.
- The line should be removed if there are any signs of vascular compromise, or as early as possible after it is no longer needed.

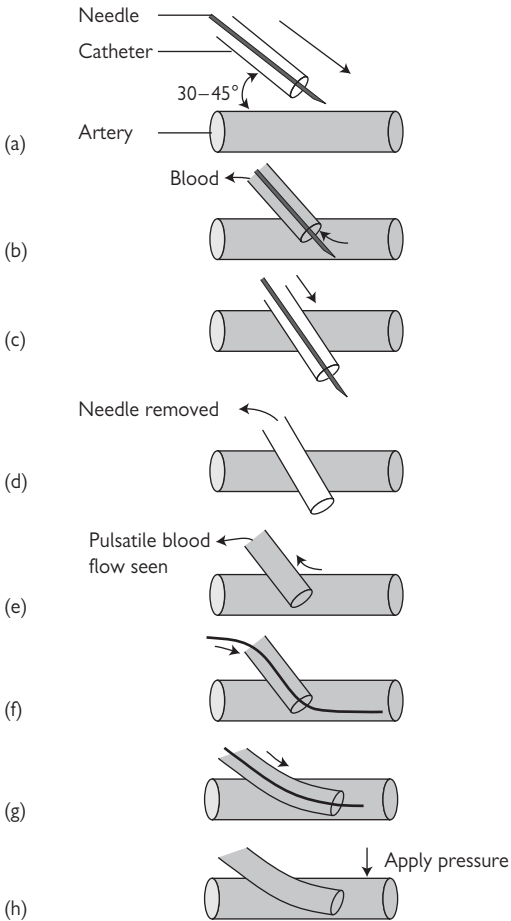


Fig. 18.1 Arterial line insertion: over-the-wire technique. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd ed. Oxford: Oxford University Press.

Arterial line insertion: over-the-needle technique (see Fig. 18.2)

- Locate and palpate the artery with the non-dominant hand (1–2 cm from the wrist between the bony head of the distal radius and the flexor carpi radialis tendon).
- The catheter and needle are advanced towards the artery at a 30–45° angle (Fig. 18.2(a)) until blood return is seen (Fig. 18.2(b)).
- The catheter and needle are then advanced slightly further and the catheter/needle angle is lowered to 10–15° (Fig. 18.2(c)).
- The catheter is advanced *over the needle* into the vessel (Fig. 18.2(d)).
- Proximal pressure is applied to the artery, the needle is removed (Fig. 18.2(e)), and the catheter is connected to the transduction system.
- Secure the catheter in place using suture or tape.
- Check perfusion to the hand after insertion of the arterial line and at frequent intervals.

Complications

- Local and systemic infection.
- Bleeding, haematoma, bruising.
- Vascular complications: blood vessel injury, pseudoaneurysm, thromboembolism, and vasospasm.
- Arterial spasm may occur after multiple unsuccessful attempts at arterial catheterization. If this occurs, use an alternative site.
- There may be difficulty in passing a wire or catheter despite the return of pulsatile blood. Adjustment of the angle, withdrawal of the needle, or a slight advance, may be helpful.

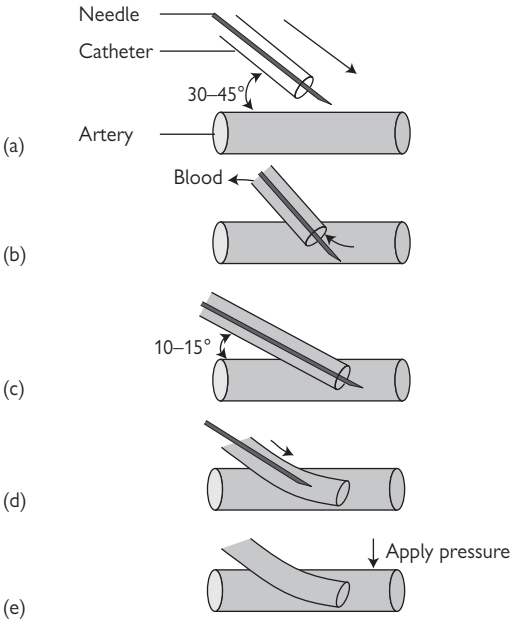


Fig. 18.2 Arterial line insertion: over-the-needle technique. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd edn. Oxford: Oxford University Press.

Central line insertion


You will need the following

- Sterile dressing pack and gloves.
- 10 mL and 5 mL syringe with green (21G) and orange (25G) needles
- Local anaesthetic (e.g. 2% lidocaine).
- Central line (e.g. 16G long Abbocath[®] or Seldinger catheter)
- Saline flush.
- Silk suture and needle.
- No. 11 scalpel blade.
- Sterile occlusive dressing (e.g. Tegaderm[®]).

Risks

- Arterial puncture (remove and apply local pressure).
- Pneumothorax (insert chest drain or aspirate if required).
- Haemothorax.
- Chylothorax (mainly left subclavian lines).
- Infection (local, septicaemia, bacterial endocarditis).
- Brachial plexus or cervical root damage (over-enthusiastic infiltration with local anaesthetic).
- Arrhythmias.

General procedure

- The basic technique is the same whatever vein is cannulated.
- Lie the patient supine (\pm head-down tilt).
- Turn the patient's head away from the side you wish to cannulate.
- Clean the skin with iodine or chlorhexidine: from the angle of the jaw to the clavicle for internal jugular vein (IJV) cannulation, and from the midline to the axilla for the subclavian approach.
- Use the drapes to isolate the sterile field.
- Flush the lumen of the central line with saline.
- Identify your landmarks (see  Central line insertion, p. 790 and Internal jugular vein cannulation, p. 792).
- Infiltrate the skin and subcutaneous tissue with local anaesthetic.
- Have the introducer needle and Seldinger guide wire within easy reach so that you can reach them with one hand without having to release your other hand. Your fingers may be distorting the anatomy slightly, making access to the vein easier, and if released it may prove difficult to relocate the vein.
- With the introducer needle in the vein, check that you can aspirate blood freely. Use the hand that was on the pulse to immobilize the needle relative to the skin and mandible or clavicle.
- Remove the syringe and pass the guide wire into the vein; it should pass freely. If there is resistance, remove the wire, check that the needle is still within the lumen, and try again.
- Remove the needle, leaving the wire within the vein and use a sterile swab to maintain gentle pressure over the site of venepuncture to prevent excessive bleeding.


- With a No. 11 blade, make a nick in the skin where the wire enters, to facilitate dilatation of the subcutaneous tissues. Pass the dilator over the wire and remove, leaving the wire *in situ*.
- Pass the central line over the wire into the vein. Remove the guide wire, flush the lumen with fresh saline, and close off to air.
- Suture the line in place and cover the skin penetration site with a sterile occlusive dressing.

Measuring the central venous pressure (CVP): tips and pitfalls

- When asked to see a patient with an abnormal CVP reading at night on the wards, it is a good habit to always re-check the zero and the reading yourself.
- Always do measurements with the mid-axillary point as the zero reference. Sitting the patient up will drop the central filling pressure (pooling in the veins).
- Fill the manometer line, being careful not to soak the cotton wool stopping. If this gets wet, it limits the free-fall of saline or dextrose in the manometer line.
- Look at the rate and character of the venous pressure. It should fall to its value quickly and swing with respiration.
- If it fails to fall quickly, consider whether the line is open (i.e. saline running in), blocked with blood clot, positional (up against the vessel wall—ask the patient to take some deep breaths), arterial blood (blood tracks back up the line). Raise the whole dripstand (if you are strong), and make sure that the level falls. If it falls when the whole stand is elevated, it may be that the CVP is very high.
- It is easier, and safer, to cannulate a central vein with the patient supine or head down. There is an increased risk of air embolus if the patient is semi-recumbent.

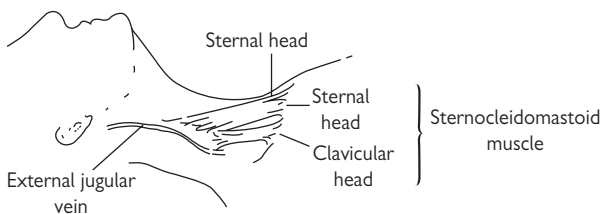
Internal jugular vein cannulation

The IJV runs just posterolateral to the carotid artery within the carotid sheath and lies medial to the sternocleidomastoid muscle (SCM) in the upper part of the neck, between the two heads of the SCM in its medial portion, and enters the subclavian vein near the medial border of the anterior scalene muscle (see Fig.18.3). There are three basic approaches to IJV cannulation: medial to SCM, between the two heads of the SCM, or lateral to the SCM. The approach used varies and depends on the experience of the operator and the institution.

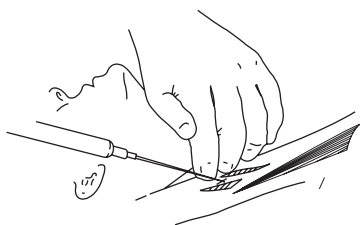
- Locate the carotid artery between the sternal and clavicular heads of the SCM at the level of the thyroid cartilage; the IJV lies just lateral and parallel to it.
- Keeping the fingers of one hand on the carotid pulsation, infiltrate the skin with local anaesthetic thoroughly, aiming just lateral to this and ensuring that you are not in a vein.
- Ideally, first locate the vein with a blue or green needle. Advance the needle at 45° to the skin, with gentle negative suction on the syringe, aiming for the ipsilateral nipple, lateral to the pulse.
- If you fail to find the vein, withdraw the needle slowly, maintaining negative suction on the syringe (you may have inadvertently transfixed the vein). Aim slightly more medially and try again.
- Once you have identified the position of the vein, change to the syringe with the introducer needle, cannulate the vein, and pass the guide wire into the vein (see  Pulmonary artery catheterization, pp. 800–5).

Tips and pitfalls

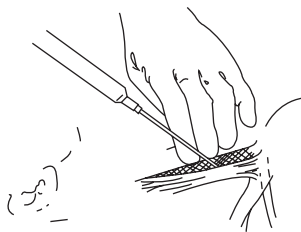
- Venous blood is dark, and arterial blood is pulsatile and bright red!
- Once you locate the vein, change to the syringe with the introducer needle, taking care not to release your fingers from the pulse; they may be distorting the anatomy slightly, making access to the vein easier, and if released it may prove difficult to relocate the vein.
- The guide wire should pass freely down the needle and into the vein. With the left IJV approach, there are several acute bends that need to be negotiated. If the guide wire keeps passing down the wrong route, ask your assistant to hold the patient's arms out at 90° to the bed, or even above the patient's head, to coax the guide wire down the correct path.
- For patients who are intubated or require respiratory support, it may be difficult to access the head of the bed. The anterior approach may be easier (see Fig. 18.3) and may be done from the side of the bed (the left side of the bed for right-handed operators, using the left hand to locate the pulse and the right to cannulate the vein).
- The IJV may also be readily cannulated with a long Abbocath®. No guide wire is necessary, but, as a result, misplacement is more common than with the Seldinger technique.
- When using an Abbocath®, on cannulating the vein, remember to advance the sheath and needle a few mm to allow the tip of the plastic sheath (~1 mm behind the tip of the bevelled needle) to enter the vein. Holding the needle stationary, advance the sheath over it into the vein.
- Arrange for a chest X-ray (CXR) to confirm the position of the line.



(a) Surface anatomy of external and internal jugular veins



(b) Anterior approach: the chin is in the midline and the skin puncture is over the sternal head of the SCM muscle



(c) Central approach: the chin is turned away and the skin puncture is between the two heads of the SCM muscle

Fig. 18.3 Internal jugular vein cannulation.

Subclavian vein cannulation

The axillary vein becomes the subclavian vein (SCV) at the lateral border of the 1st rib and extends for 3–4 cm just deep to the clavicle. It is joined by the ipsilateral IJV to become the brachiocephalic vein behind the sternoclavicular joint (see Fig. 18.4). The subclavian artery and brachial plexus lie posteriorly, separated from the vein by the scalenus anterior muscle. The phrenic nerve and the internal mammary artery lie behind the medial portion of the SCV and, on the left, lies the thoracic duct.

- Select the point 1 cm below the junction of the medial third and middle third of the clavicle. If possible, place a bag of saline between the scapulae to extend the spine.
- Clean the skin with iodine or chlorhexidine.
- Infiltrate the skin and subcutaneous tissue and periosteum of the inferior border of the clavicle with local anaesthetic up to the hilt of the green (21G) needle, ensuring that it is not in a vein.
- Insert the introducer needle with a 10 mL syringe, guiding gently under the clavicle. It is safest to initially hit the clavicle, and 'walk' the needle under it until the inferior border is just cleared. In this way you keep the needle as superficial to the dome of the pleura as possible. Once it has just skimmed underneath the clavicle, advance it slowly towards the contralateral sternoclavicular joint, aspirating as you advance. Using this technique, the risk of pneumothorax is small, and success is high.
- Once the venous blood is obtained, rotate the bevel of the needle towards the heart. This encourages the guide wire to pass down the brachiocephalic vein rather than up the IJV.
- The wire should pass easily into the vein. If there is difficulty, try advancing during the inspiratory and expiratory phases of the respiratory cycle.
- Once the guide wire is in place, remove the introducer needle, and pass the dilator over the wire. When removing the dilator, note the direction that it faces; it should be slightly curved downwards. If it is slightly curved upwards, then it is likely that the wire has passed up into the IJV. The wire may be manipulated into the brachiocephalic vein under fluoroscopic control but, if this is not available, it is safer to remove the wire and start again.
- After removing the dilator, pass the central venous catheter over the guide wire, remove the guide wire, and secure as above.
- A CXR is mandatory after subclavian line insertion, to exclude a pneumothorax and to confirm satisfactory placement of the line, especially if fluoroscopy was not employed.

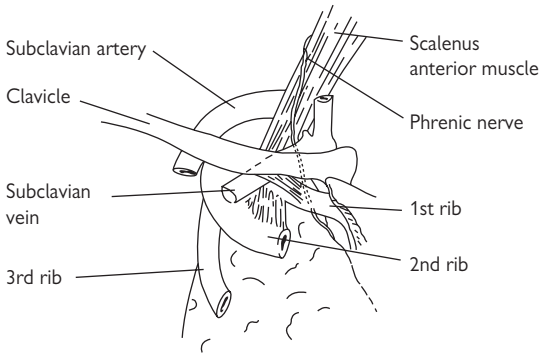


Fig. 18.4 The subclavian vein and surrounding structures.

Ultrasound-guided central venous catheterization (1)

Traditional central venous catheterization methods rely on anatomical landmarks to predict vein position. However, the relationship between such landmarks and vein position varies significantly in 'normal' individuals. Failure and complication rates using landmark methods are significant, and therefore serious complications may occur. Recent advances in portable ultrasound equipment have now made it possible to insert central venous catheters under two-dimensional (2D) ultrasound guidance.

Advantages of this technique include:

- identification of the actual and relative vein position
- identification of anatomical variations
- confirmation of target vein patency.

Guidelines from the National Institute for Clinical Excellence (September 2002) state: 'Two-dimensional imaging ultrasound guidance is recommended as the preferred method for insertion of central venous catheters into the internal-jugular vein (IJV) in adults and children in elective situations'. However, training and equipment availability render such recommendations effectively useless in the UK at present.

Equipment/personnel needed

- Standard Seldinger-type kit or whatever is locally available.
- An assistant is essential.
- Ultrasound equipment:
 - screen: displays 2D ultrasound image of anatomical structures.
 - sheaths: dedicated, sterile sheaths of PVC or latex, long enough to cover the probe and connecting cable (a rubber band secures the sheath to the probe).
 - probe: transducer which emits and receives ultrasound information to be processed for display; marked with an arrow or notch for orientation.
 - power: battery or mains.
 - sterile gel: transmits ultrasound and provides good interface between patient and probe.

Preparation

Perform a preliminary non-sterile scan to access each IJV for patency and size.

Patient

Sterile precautions should be taken with patient's head turned slightly away from the cannulation site. Head-down tilt (if tolerated) or leg elevation should be used to increase the filling and size of the IJV. Ensure adequate drapes to maintain a sterile field.

Excessive head rotation or extension may decrease the diameter of the vein.

Ultrasound equipment

- Ensure that the display can be seen.
- The sheath is opened (operator) and gel squirted in (assistant).
A generous amount of gel ensures good contact and air-free coupling between the probe tip and sheath. Too little may compromise image quality.
- The probe and connecting cable are lowered into the sheath (assistant), which is then unrolled along them (operator).
- A rubber band secures the sheath to the probe.
- The sheath over the probe tip is smoothed out (wrinkles will degrade image quality).
- Apply liberal amounts of gel to the sheathed probe tip for good ultrasound transmission and increased patient comfort during movement.

Ultrasound-guided central venous catheterization (2)

Scanning

The most popular scanning orientation for IJV central catheter placement is the transverse plane:

- apply the probe tip *gently* to the neck lateral to the carotid pulse at the cricoid level or in the sternomastoid-clavicular triangle.
- keep the probe perpendicular at all times, with the tip flat against the skin.
- orientate the probe so that movement to the left ensures that the display looks to the left (and vice versa). Probes are usually marked to help orientation. By convention, the mark should be to the patient's right (transverse plane) or to the head (longitudinal scan). The marked side appears on the screen as a bright dot.
- if the vessels are not immediately visible, keep the probe perpendicular and gently glide medially or laterally until they are found.

When moving the probe, watch the screen—not your hands.

After identification of the internal jugular vein

- Position the probe so that the IJV is shown at the display's horizontal midpoint.
- Keep the probe immobile.
- Direct the needle (bevel towards probe) caudally under the marked midpoint of the probe tip at approximately 60° to the skin.
- The needle bevel faces the probe to help direct the guide wire down the IJV later.
- Advance the needle towards the IJV.

Needle passage causes a 'wavefront' of tissue compression. This is used to judge the progress of the needle and position. Absence of visible tissue reaction indicates incorrect needle placement. Just before vessel entry, 'tenting' of the vein is usually observed.

One of the most difficult aspects to learn initially, is the steep needle angulation required, but this ensures that the needle enters the IJV in the ultrasound (US) beam and takes the shortest and most direct route through the tissues.

Needle pressure may oppose the vein walls, resulting in vein transfixion. Slow withdrawal of the needle with continuous aspiration can help result in lumen access.

Pass the guide wire into the jugular vein in the usual fashion.

Re-angling the needle from 60° to a shallower angle, e.g. 45°, may help guide-wire feeding. Scanning the vein in the longitudinal plane may demonstrate the catheter in the vessel but after securing and dressing the central venous catheter (CVC), an X-ray should still be obtained to confirm the CVC position, and exclude pneumothorax.

The most common error in measurement of CVP, particularly in CVP lines that have been in place for some time, is due to partial or complete line blockade. With the manometer connected, ensure that the line is

free flowing; minor blockages can be removed by squeezing the rubber bung, with the proximal line being obliterated by acute angulation (i.e. bend the tube proximally). Measure the CVP at the mid-axillary line with the patient supine. CVP falls with upright or semi-upright recumbency, regardless of the reference point. If the CVP is high, lift the stand that holds the manometer so that the apparent CVP falls by 10 cm or so, and replace the CVP stand to ground level. If the saline or manometer reading rises to the same level, then the CVP reading is accurate. In other words, one ensures that the CVP manometer level both falls to and rises to the same level.

Pulmonary artery catheterization (1)

Indications

Pulmonary artery (PA) catheters (Swan–Ganz catheters) allow direct measurement of a number of haemodynamic parameters that aid clinical decision making in critically ill patients (evaluate right and left ventricular function, guide treatment, and provide prognostic information). The catheter itself has no therapeutic benefit and there have been a number of studies showing increased mortality (and morbidity) with their use. Consider inserting a PA catheter in any critically ill patient, after discussion with an experienced physician about whether the measurements will influence decisions on therapy (and not just to reassure yourself). Careful and frequent clinical assessment of the patient should always accompany measurements, and PA catheterization should not delay treatment of the patient.

General indications (not a comprehensive list) include:

- management of complicated myocardial infarction (MI).
- assessment and management of shock.
- assessment and management of respiratory distress (cardiogenic vs. non-cardiogenic pulmonary oedema).
- evaluation of the effects of treatment in unstable patients (e.g. inotropes, vasodilators, mechanical ventilation, etc.).
- delivering therapy (e.g. thrombolysis for pulmonary embolism, prostacyclin for pulmonary hypertension, etc.).
- assessment of fluid requirements in critically ill patients.

Equipment required

- Full resuscitation facilities should be available and the patient's electrocardiogram (ECG) should be continuously monitored.
- Bag of heparinized saline for flushing the catheter and transducer set for pressure monitoring. (Check that your assistant is experienced in setting up the transducer system BEFORE you start.)
- 8F introducer kit (pre-packaged kits contain the introducer sheath and all the equipment required for central venous cannulation).
- PA catheter: commonly a triple-lumen catheter, that allows simultaneous measurement of right atrial (RA) pressure (proximal port) and PA pressure (distal port) and incorporates a thermistor for measurement of cardiac output by thermodilution. Check your catheter before you start.
- Fluoroscopy is preferable, though not essential.

General technique (see Fig. 18.5)

- Do not attempt this without supervision if you are inexperienced.
- Observe strict aseptic technique using sterile drapes, etc.
- Insert the introducer sheath (at least 8F in size) into either the internal jugular or subclavian vein in the standard way. Flush the sheath with saline and secure to the skin with sutures.
- Do not attach the plastic sterile expandable sheath to the introducer yet but keep it sterile for use later once the catheter is in position (the catheter is easier to manipulate without the plastic covering).

- Flush all the lumens of the PA catheter and attach the distal lumen to the pressure transducer. Check the transducer is zeroed (conventionally to the mid-axillary point). Check the integrity of the balloon by inflating it with the syringe provided (1–2 mL air), and then deflate the balloon.

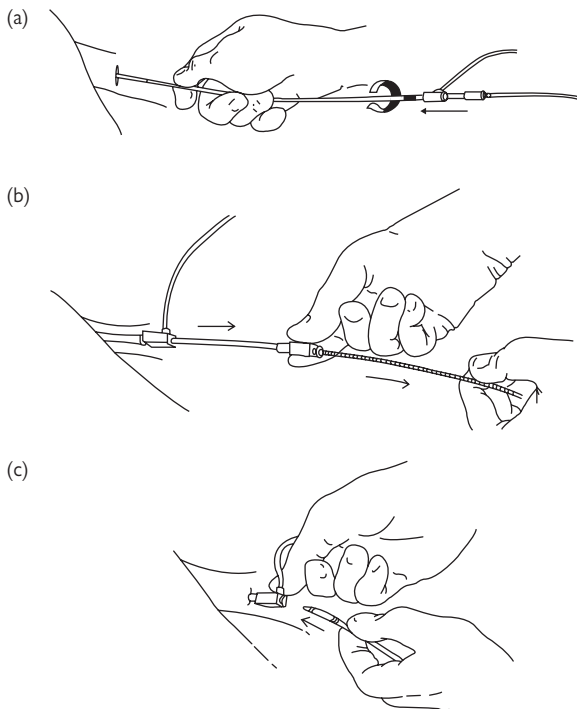


Fig. 18.5 Pulmonary artery catheterization. (a) The sheath and dilator are advanced into the vein over the guide wire. A twisting motion makes insertion easier. (b) The guide wire and dilator are then removed. The sheath has a haemostatic valve at the end preventing leakage of blood. (c) The PA catheter is then inserted through the introducer sheath into the vein.

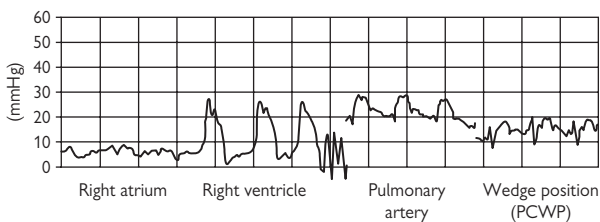
Pulmonary artery catheterization (2)

Insertion technique

- Flush all the lumens of the PA catheter and attach the distal lumen to the pressure transducer. Check the transducer is zeroed (conventionally to the mid-axillary point). Check the integrity of the balloon by inflating it with the syringe provided and then deflate the balloon.
- Pass the tip of the PA catheter through the plastic sheath, keeping the sheath compressed. The catheter is easier to manipulate without the sheath over it; once in position, extend the sheath over the catheter to keep it sterile.
- With the balloon deflated, advance the tip of the catheter to approx 10–15 cm from the right IJV or SCV, 15–20 cm from the left (the markings on the side of the catheter are at 10 cm intervals: 2 lines = 20 cm). Check that the pressure tracing is typical of the right atrial pressure (Fig. 18.6).
- Inflate the balloon and advance the catheter gently. The flow of blood will carry the balloon (and catheter) across the tricuspid valve, through the right ventricle and into the pulmonary artery (see Fig. 18.5).
- Watch the ECG tracing closely whilst the catheter is advanced. The catheter commonly triggers runs of ventricular tachycardia (VT) when crossing the tricuspid valve and through the right ventricle (RV). The VT is usually self-limiting, but should not be ignored. Deflate the balloon, pull back, and try again.
- If more than 15 cm of catheter is advanced into the RV without the tip entering the PA, this suggests the catheter is coiling in the RV. Deflate the balloon, withdraw the catheter into the RA, reinflate the balloon, and try again using clockwise torque while advancing in the ventricle, or flushing the catheter with cold saline to stiffen the plastic. If this fails repeatedly, try under fluoroscopic guidance.
- As the tip passes into a distal branch of the PA, the balloon will impact and not pass further—the wedge position—and the pressure tracing will change (see Fig. 18.6).
- Deflate the balloon and check that a typical PA tracing is obtained. If not, try flushing the catheter lumen, and if that fails, withdraw the catheter until the tip is within the PA and begin again.
- Reinflate the balloon slowly. If the pulmonary capillary wedge pressure (PCWP) is seen before the balloon is fully inflated, it suggests the tip has migrated further into the artery. Deflate the balloon, withdraw the catheter 1–2 cm, and try again.
- If the pressure tracing flattens and then continues to rise, you have 'overwedged'. Deflate the balloon, pull the catheter back 1–2 cm, and start again.
- When a stable position has been achieved, extend the plastic sheath over the catheter and secure it to the introducer sheath. Clean any blood from the skin insertion site with antiseptic, and secure a coil of the PA catheter to the patient's chest to avoid inadvertent removal.
- Obtain a CXR to check the position of the catheter. The tip of the catheter should ideally be no more than 3–5 cm from the midline.

Normal values of right heart pressures and flows

Right atrial pressure	0–8 mmHg
Right ventricle	
systolic	15–30 mmHg
end diastolic	0–8 mmHg
Pulmonary artery	
systolic/diastolic	15–30/4–12 mmHg
mean	9–16 mmHg
PCWP	2–10 mmHg
Cardiac index	2.8–4.2 L/min/m ²

**Fig. 18.6** Pressure tracings during pulmonary artery catheterization.

Pulmonary artery catheterization (3)

Tips and pitfalls

- Never withdraw the catheter with the balloon inflated.
- Never advance the catheter with the balloon deflated.
- Never inject liquid into the balloon.
- Never leave the catheter with the balloon inflated, as pulmonary infarction may occur.
- The plastic of the catheter softens with time at body temperature and the tip of the catheter may migrate further into the PA branch. If the pressure tracing with the balloon deflated is 'partially wedged' (and flushing the catheter does not improve this), withdraw the catheter 1–2 cm and reposition.
- Sometimes it is impossible to obtain a wedged trace. In this situation, one has to use the PA diastolic pressure as a guide. In health there is ~2–4 mmHg difference between PA diastolic pressure and PCWP. Any condition that causes pulmonary hypertension (e.g. severe lung disease, acute respiratory distress syndrome (ARDS), longstanding valvular disease) will alter this relationship.
- *Valvular lesions, ventricular septal defects (VSDs), prosthetic valves, and pacemakers:* if these are present then seek advice from a cardiologist. The risk of subacute bacterial endocarditis (SBE) may be sufficiently great that the placement of a PA catheter may be more detrimental than beneficial.
- *Positive end-expiratory pressure (PEEP):* measurement and interpretation of PCWP in patients on PEEP depends on the position of the catheter. Ensure the catheter is below the level of the left atrium on a lateral CXR. Removing PEEP during measurement causes marked fluctuations in haemodynamics and oxygenation and the pressures do not reflect the state once back on the ventilator.

Complications

- *Arrhythmias:* watch the ECG tracing closely while the catheter is advanced. The catheter commonly triggers runs of VT when crossing the tricuspid valve and through the RV. If this happens, deflate the balloon, pull back, and try again. The VT is usually self-limiting, but should not be ignored.
- *Pulmonary artery rupture (~0.2% in one series):* damage may occur if the balloon is overinflated in a small branch. Risk factors include mitral valve disease (large v wave confused with poor wedging), pulmonary hypertension, multiple inflations or hyperinflations of the balloon. Haemoptysis is an early sign. It is safer to follow PA diastolic pressures if these correlate with the PCWP.
- Pulmonary infarction.
- *Knots:* these usually occur at the time of initial placement in patients where there has been difficulty in traversing the RV. Signs include loss of pressure tracing, persistent ectopy, and resistance to catheter manipulation. If this is suspected, stop manipulation and seek expert help.

- *Infection*: risks increase with the length of time the catheter is left *in situ*. The pressure transducer may occasionally be a source of infection. Remove the catheter and introducer, and replace only if necessary.
- *Other complications*: complications associated with central line insertion, thrombosis and embolism, balloon rupture, intracardiac damage.

Indications for temporary pacing

1. Following acute myocardial infarction

- Asystole.
- Symptomatic complete heart block (CHB) (any territory).
- Symptomatic 2° heart block (any territory).
- Trifascicular block—alternating left and right bundle branch block (LBBB and RBBB).
 - 1° heart block + RBBB + left anterior descending artery (LAD).
 - new RBBB and left posterior hemiblock.
 - LBBB and long PR interval.
- After anterior MI.
 - asymptomatic CHB.
 - asymptomatic 2° (Mobitz II) block.
- Symptomatic sinus bradycardia unresponsive to atropine.
- Recurrent VT for atrial or ventricular overdrive pacing.


2. Unrelated to myocardial infarction

- Symptomatic sinus or junctional bradycardia that is unresponsive to atropine (e.g. carotid sinus hypersensitivity).
- Symptomatic 2° heart block or sinus arrest.
- Symptomatic complete heart block.
- Torsades de pointes tachycardia.
- Recurrent VT for atrial or ventricular overdrive pacing.
- Bradycardia-dependent tachycardia.
- Drug overdose (e.g. verapamil, β -blockers, digoxin).
- Permanent pacemaker box change in a pacing-dependent patient.

3. Before general anaesthesia

- The same principles as for acute MI (see above).
- Sinoatrial disease and 2° (Wenckebach) heart block only need prophylactic pacing if there are symptoms of syncope or pre-syncope.
- Complete heart block.

Transvenous temporary pacing

- The technique of temporary wire insertion is described on  Temporary ventricular pacing, p. 808.
- The most commonly used pacing mode and the mode of choice for life-threatening bradyarrhythmias is ventricular demand pacing with a single bipolar wire positioned in the right ventricle.
- In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with RV infarction), cardiac output may be increased by up to 20% by maintaining atrioventricular (AV) synchrony. This requires two pacing leads, one atrial and one ventricular, and a dual pacing box.

Epicardial temporary pacing

- Following cardiac surgery, patients may have *epicardial wires* (attached to the pericardial surface of the heart) left in for up to 1 week in case of postoperative bradyarrhythmia. These are used in the same way as transvenous pacing wires, but the threshold may be higher.

Indications for temporary transvenous cardiac pacing

Emergency/acute

- Acute myocardial infarction: (class I: American College of Cardiology/American Heart Association (ACC/AHA)).³
- Asystole.
- Symptomatic bradycardia (sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine).
- Bilateral bundle branch block (alternating BBB or RBBB with alternating left anterior/left posterior hemiblock (LAHB/LPHB)).
- New or indeterminate age bifascicular block with first-degree AV block.
- Mobitz type II second-degree AV block.

Bradycardia not associated with acute myocardial infarction

- Asystole.
- Second or third-degree AV block with haemodynamic compromise or syncope at rest.
- Ventricular tachyarrhythmias secondary to bradycardia.

Elective


- Support for procedures that may promote bradycardia.
- General anaesthesia with:
 - 2nd- or 3rd-degree AV block.
 - Intermittent AV block.
 - 1st degree AV block with bifascicular block.
 - 1st degree AV block and LBBB.
- Cardiac surgery.
 - Aortic surgery.
 - Tricuspid surgery.
 - VSD closure.
 - Ostium primum repair.

Rarely considered for coronary angioplasty (usually to right coronary artery)

Overdrive suppression of tachyarrhythmias

Reproduced with permission from Gammage MD (2000). Temporary cardiac pacing. *Heart* **83**: 715–20.

Atrioventricular sequential pacing

In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with RV infarction), cardiac output may be increased by up to 20% by maintaining AV synchrony. This requires two pacing leads, one atrial and one ventricular, and a dual pacing box (see  DC cardioversion: special situations, p. 821).

Temporary ventricular pacing

- *Cannulate a central vein:* the wire is easiest to manipulate via the right internal jugular (RIJ) approach but is more comfortable for the patient via the right subclavian (SC) vein. The left internal jugular (LIJ) approach is best avoided as there are many acute bends to negotiate and it is difficult to achieve a stable position. Avoid the left subclavicular area as this is the preferred area for permanent pacemaker insertion and should be kept 'virgin' if possible. The femoral vein may be used (incidence of deep vein thrombosis (DVT) and infection is high).
- *Insert a sheath* (similar to that for PA catheterization) through which the pacing wire can be fed. Pacing wires are commonly 5F or 6F, and a sheath at least one size larger is necessary. Most commercially available pacing wires are pre-packed with an introducer needle and plastic cannula similar to an Abbocath[®], which may be used to position the pacing wire. However, the cannula does not have a haemostatic seal. The plastic cannula may be removed from the vein, leaving the bare wire entering the skin, once a stable position has been achieved. This reduces the risk of wire displacement but also makes repositioning of the wire more difficult should this be necessary, and infection risk is higher.
- Pass the wire through the sterile plastic cover that accompanies the introducer sheath, and advance it into the upper right atrium (see Fig. 18.7) but do not unfurl the cover yet. The wire is much easier to manipulate with gloved hands without the hindrance of the plastic cover.
- Advance the wire with the tip pointing towards the right ventricle; it may cross the tricuspid valve easily. If it fails to cross, point the tip to the lateral wall of the atrium and form a loop. Rotate the wire and the loop should fall across the tricuspid valve into the ventricle.
- Advance and rotate the wire so that the tip points inferiorly as close to the tip of the right ventricle (laterally) as possible.
- If the wire does not rotate down to the apex easily, it may be because you are in the coronary sinus rather than in the right ventricle. (The tip of the wire points to the left shoulder). Withdraw the wire and recross the tricuspid valve.
- Leave some slack in the wire; the final appearance should be like the outline of a sock, with the 'heel' in the right atrium, the 'arch' over the tricuspid, and the 'big toe' at the tip of the right ventricle.
- Connect the wire to the pacing box and check the threshold. Ventricular pacing thresholds should be <1.0 V but a threshold up to 1.5 V is acceptable if another stable position cannot be achieved.
- Check for positional stability. With the box pacing at a rate higher than the intrinsic heart rate, ask the patient to take some deep breaths, cough forcefully, and sniff. Watch for failure of capture and, if this occurs, reposition the wire.
- Set the output to 3 V and the box on 'demand'. If the patient is in sinus rhythm and has an adequate blood pressure, set the box rate to just below the patient's rate. If there is complete heart block or bradycardia, set the rate at 70–80/min.
- Cover the wire with the plastic sheath and suture the sheath and wire securely to the skin. Loop the rest of the wire and fix to the patient's skin with adhesive dressing.

- When the patient returns to the ward, obtain a CXR to confirm satisfactory positioning of the wire and to exclude a pneumothorax.

Checklist for pacing wire insertion

- Check the screening equipment and defibrillator are working.
- Check the type of pacing wire: atrial wires have a pre-formed 'J' that allows easy placement in the atrium or appendage and is very difficult to manipulate into a satisfactory position in the ventricle. Ventricular pacing wires have a more open, gentle 'J'.
- Check the pacing box (single vs. dual or sequential pacing box) and leads to attach to the wire(s). Familiarize yourself with the controls on the box: you may need to connect up in a hurry if the patient's intrinsic rhythm slows further.
- Remember to don the lead apron before wearing the sterile gown, mask and gloves.

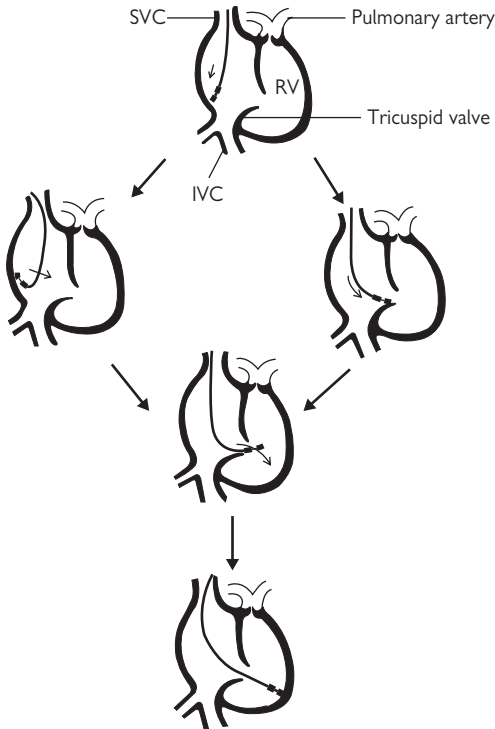


Fig. 18.7 Insertion of a ventricular pacing wire (see text for details) Reproduced with permission from Ramrakha P, Moore K (2004). *Oxford Handbook of Acute Medicine*. 2nd edn. Oxford: Oxford University Press.

Temporary atrial pacing

- The technique of inserting an atrial temporary wire is similar to that of ventricular pacing.
- Advance the atrial wire until the 'J' is reformed in the right atrium.
- Rotate the wire and withdraw slightly to position the tip in the right atrial appendage. Aim for a threshold of <1.5 V.
- If atrial wires are not available, a ventricular pacing wire may be manipulated into a similar position or passed into the coronary sinus for left atrial pacing.

Atrioventricular sequential pacing

In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with right ventricular infarction), cardiac output may be increased by up to 20% by maintaining atrioventricular synchrony. This requires two pacing leads, one atrial and one ventricular, and a dual pacing box.

Patients most likely to benefit from AV sequential pacing

- Acute MI (especially RV infarction).
- 'Stiff' left ventricle: aortic stenosis, hypertrophic cardiomyopathy (HCM), hypertensive heart disease, amyloidosis.
- Low cardiac output states (cardiomyopathy).
- Recurrent atrial arrhythmias.

Temporary pacing: complications

Ventricular ectopics or VT

- Non-sustained VT is common as the wire crosses the tricuspid valve (especially in patients receiving an isoprenaline infusion) and does not require treatment.
- Try to avoid long runs of VT and, if necessary, withdraw the wire into the atrium and wait until the rhythm has settled.
- If ectopics persist after the wire is positioned, try adjusting the amount of slack in the wire in the region of the tricuspid valve (either more or less).
- Pacing the right ventricular outflow tract (RVOT) can provoke runs of VT.

Failure to pace and/or sense

- It is difficult to get low pacing thresholds (<1.0 V) in patients with extensive MI (especially of the inferior wall) or cardiomyopathy, or who have received class I antiarrhythmic drugs. Accept a slightly higher value if the position is otherwise stable and satisfactory.
- If the position of the wire appears satisfactory and yet the pacing thresholds are high, the wire may be in a left hepatic vein. Pull the wire back into the atrium and try again, looking specifically for the ventricular ectopics as the wire crosses the tricuspid valve.
- The pacing threshold commonly doubles in the first few days due to endocardial oedema.
- If the pacemaker suddenly fails, the most common reason is usually wire displacement.
- Increase the pacing output of the box.
- Check all the connections of the wire and the battery of the box.
- Try moving the patient to the left lateral position until arrangements can be made to reposition the wire.

Perforation

- A pericardial rub may be present in the absence of perforation (especially post-MI).
- *Presentation:* pericardial chest pain, increasing breathlessness, falling blood pressure, enlarged cardiac silhouette on CXR, signs of cardiac tamponade, left diaphragmatic pacing at low output.
- *Management:*
 - if there are signs of cardiac tamponade arrange for urgent echocardiography (ECHO) and reposition the wire.
 - monitor the patient carefully over the next few days, with repeat ECHOs to detect incipient cardiac tamponade.

Diaphragmatic pacing

- High-output pacing (10 V), even with a satisfactory position of the ventricular lead may cause pacing of the left hemidiaphragm. At low voltages, this suggests perforation (see above).
- Right hemidiaphragm pacing may be seen with atrial pacing and stimulation of the right phrenic nerve.
- Reposition the wire if symptomatic (painful twitching, dyspnoea).

Complications of temporary pacing

- Complications associated with central line insertion
- Ventricular ectopics
- Non-sustained VT
- Perforation
- Pericarditis
- Diaphragmatic pacing
- Infection
- Pneumothorax
- Cardiac tamponade

Pericardial aspiration (1)

Equipment

Establish peripheral venous access and check that full facilities for resuscitation are available. Pre-prepared pericardiocentesis sets may be available. You will need:

- trolley as for central line insertion, with iodine or chlorhexidine for skin, dressing pack, sterile drapes, local anaesthetic (lidocaine 2%), syringes (including a 50 mL), needles (25G and 22G), No. 11 blade, and silk sutures.
- pericardiocentesis needle (15 cm, 18G) or similar Wallace cannula.
- J guide wire (≥ 80 cm, 0.035 diameter).
- dilators (up to 7 Fr).
- pigtail catheter (≥ 60 cm with multiple sideholes, a large Seldinger-type CVP line can be used if no pigtail is available).
- drainage bag and connectors.
- facilities for fluoroscopy or echocardiographic screening.

Technique (see Fig. 18.8)

- Position the patient at $\sim 30^\circ$. This allows the effusion to pool inferiorly within the pericardium.
- Sedate the patient lightly with midazolam (2.5–7.5 mg IV) and fentanyl 50–200 mcg IV if necessary. Use with caution as this may drop the blood pressure (BP) in patients already compromised by the effusion.
- Wearing a sterile gown and gloves, clean the skin from mid-chest to mid-abdomen and put the sterile drapes on the patient.
- Infiltrate the skin and subcutaneous tissues with local anaesthetic starting 1–1.5 cm below the xiphisternum and just to the left of the midline, aiming for the left shoulder and staying as close to the inferior border of the rib cartilages as possible.
- The pericardiocentesis needle is introduced into the angle between the xiphisternum and the left costal margin angled at $\sim 30^\circ$. Advance slowly, aspirating gently, and then injecting more lidocaine every few millimetres, aiming for the left shoulder.
- As the parietal pericardium is pierced, you may feel a 'give' and fluid will be aspirated. Remove the syringe and introduce the guide wire through the needle.
- Check the position of the guide wire by screening. It should loop within the cardiac silhouette only and not advance into the superior vena cava (SVC) or PA.
- Remove the needle, leaving the wire in place. Enlarge the skin incision slightly using the blade, and dilate the track.
- Insert the pigtail over the wire into the pericardial space and remove the wire.
- Take specimens for microscopy, culture (and inoculate a sample into blood culture bottles), cytology, and haematocrit if blood stained (a full blood count (FBC) tube; ask the haematologists to run on the Coulter counter for rapid estimation of Hb).

- Aspirate to dryness watching the patient carefully. Symptoms and haemodynamics (tachycardia) often start to improve with removal of as little as 100 mL of pericardial fluid.
- If the fluid is heavily blood stained, withdraw fluid cautiously—if the pigtail is in the right ventricle, withdrawal of blood may cause cardiovascular collapse. Arrange for urgent Hb/haematocrit.
- Leave on free drainage and attached to the drainage bag.
- Suture the pigtail to the skin securely and cover with a sterile occlusive dressing.

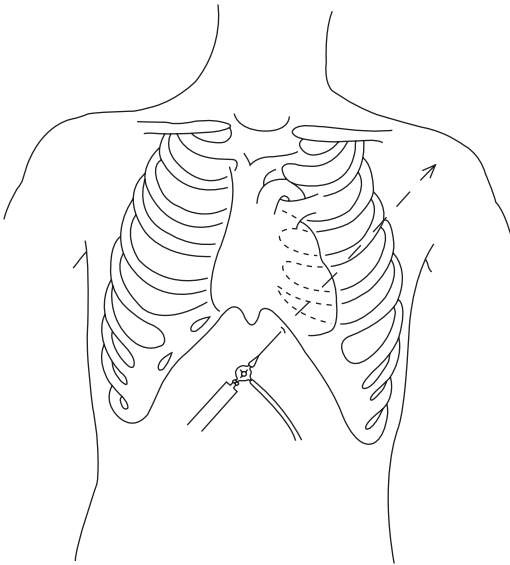


Fig. 18.8 Pericardial aspiration. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd ed. Oxford: Oxford University Press.

Aftercare

- Closely observe the patient for recurrent tamponade (obstruction of drain) and repeat ECHO.
- Discontinue anticoagulants.
- Remove the drain after 24 hours or when the drainage stops.
- Consider the need for surgery (drainage, biopsy or pericardial window) or specific therapy (chemotherapy if malignant effusion, antimicrobials if bacterial, dialysis if renal failure, etc.).

Pericardial aspiration (2)

Tips and pitfalls

- If the needle touches the heart's epicardial surface, you may feel a 'ticking' sensation transmitted down the needle: withdraw the needle a few millimetres, angulate the needle more superficially, and try cautiously again, aspirating as you advance.
- If you do not enter the effusion, and the heart is not encountered:
 - withdraw the needle slightly and advance again, aiming slightly deeper, but still towards the left shoulder.
 - if this fails, try again, aiming more medially (mid-clavicular point or even suprasternal notch).
 - consider trying the apical approach (starting laterally at the cardiac apex and aiming for the right shoulder), if ECHO confirms sufficient fluid at the cardiac apex.
- If available, *intrathoracic ECG* can be monitored by a lead attached to the needle as it is advanced. This is seldom clinically useful in our experience. Penetration of the myocardium results in ST elevation, suggesting the needle has been advanced too far.
- *Difficulty in inserting the pigtail*:
 - this may be because of insufficient dilatation of the tract (use a larger dilator).
 - holding the wire taught (by gentle traction) while pushing the catheter may help; take care not to pull the wire out of the pericardium.
- *Haemorrhagic effusion vs. blood*:
 - compare the Hb of the pericardial fluid to the venous blood Hb
 - place some of the fluid in a clean container; blood will clot, whereas haemorrhagic effusion will not, as the 'whipping' action of the heart tends to defibrinate it.
 - confirm the position of the needle by first withdrawing some fluid and then injecting 10–20 mL of contrast; using fluoroscopy; see if the contrast stays within the cardiac silhouette.
 - alternatively, if using ECHO guidance, inject 5–10 mL saline into the needle, looking for 'microbubble contrast' in the cavity containing the needle tip. Injecting 20 mL saline rapidly into a peripheral vein will produce 'contrast' in the RA and RV, and may allow them to be distinguished from the pericardial space.
 - connect a pressure line to the needle; a characteristic waveform will confirm penetration of the RV.

Complications of pericardiocentesis

- Penetration of a cardiac chamber (usually right ventricle).
- Laceration of an epicardial vessel.
- Arrhythmia (atrial arrhythmias as the wire is advanced, ventricular arrhythmias if the RV is penetrated).
- Pneumothorax.
- Perforation of abdominal viscus (liver, stomach, colon).
- Ascending infection.

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DC cardioversion

Relative contraindications

- Digoxin toxicity.
- Electrolyte disturbance ($\downarrow\text{Na}^+$, $\downarrow\text{K}^+$, $\downarrow\text{Ca}^{2+}$, $\downarrow\text{Mg}^{2+}$, acidosis).
- Inadequate anticoagulation and chronic atrial fibrillation (AF).

Checklist for DC cardioversion

- | | |
|---------------------|--|
| • Defibrillator: | Check this is functioning with a fully equipped arrest trolley to hand in case of arrest. |
| • Informed consent: | Unless life-threatening emergency. |
| • 12-lead ECG: | AF, flutter, SVT, VT, signs of ischaemia or digoxin. If ventricular rate is slow have an external (transcutaneous) pacing system nearby in case of asystole. |
| • Nil by mouth: | For at least 4 hours. |
| • Anticoagulation: | Does the patient require anticoagulants? Is the international normalized ratio (INR) >2.0 ? (Has it been so for >3 weeks?) |
| • Potassium: | Check this is >3.5 mmol/L. |
| • Digoxin: | Check there are no features of digoxin toxicity. If taking ≥ 250 mcg/day, check that renal function and recent digoxin level are normal. If there are frequent ventricular ectopics, give IV Mg^{2+} 8 mmol. |
| • Thyroid function: | Treat thyrotoxicosis or myxoedema first. |
| • IV access: | Peripheral venous cannula. |
| • Sedation: | Short general anaesthesia (propofol) is preferable to sedation with benzodiazepine and fentanyl. Bag the patient with 100% oxygen. |
| • Select energy: | (see box opposite). |
| • Synchronization: | Check this is selected on the defibrillator for all shocks (unless the patient is in VF or haemodynamically unstable). Adjust the ECG gain so that the machine is only sensing QRS complexes and not P or T waves. |

- **Paddle placement:** Most centres now use 'hands-free' adhesive pads for DC cardioversion. Some continue with the traditional hand-held paddles. Conductive gel pads should be placed between the paddles and the skin. Position one just to the right of the sternum and the other to the left of the left nipple (anterior-mid-axillary line). Alternatively, place one anteriorly just left of the sternum, and one posteriorly to the left of midline. There is some evidence that the anteroposterior (AP) position is superior for AF.

- **Cardioversion:** Check no one is in contact with the patient or with the metal bed. Ensure your own legs are clear of the bed!
Apply firm pressure on the paddles.

- **Unsuccessful:** Double the energy level and repeat up to 360 J. Consider changing the paddle position. If there is prolonged sinus pause or ventricular arrhythmia during an elective procedure, stop.

- **Successful:** Repeat ECG. Place in recovery position until awake. Monitor for 2–4 h and ensure effects of sedation have passed. Patients should be accompanied home by a friend or relative if being discharged.

Complications of DC cardioversion

- Asystole/bradycardias
- Ventricular fibrillation
- Thromboembolism
- Transient hypotension
- Skin burns
- Aspiration pneumonitis.

Suggested initial energies for DC shock for elective cardioversion

- | | | |
|-----------------------|----------|--------------|
| ● Sustained VT | 200 J | Synchronized |
| ● Atrial fibrillation | 50–100 J | Synchronized |
| ● Atrial flutter | 50 J | Synchronized |
| ● Other SVTs | 50 J | Synchronized |
- If the initial shock is unsuccessful, increase the energy (50, 100, 200, 360 J) and repeat.
 - If still unsuccessful, consider changing the paddle position and try 360 J again. It is inappropriate to persist further with elective DC cardioversion.

Anticoagulation

The risk of thromboembolism in patients with chronic AF and dilated cardiomyopathy is 0–7%, depending on the underlying risk factors.

<i>Increased risk</i>	<i>Low risk</i>
<ul style="list-style-type: none">• Prior embolic event• Mechanical heart valve• Mitral stenosis• Dilated left atrium	<ul style="list-style-type: none">• Age <60 years• No underlying heart disease• Recent onset AF (<3 days)

Anticoagulate patients at risk, with warfarin for at least 3–4 weeks. For recent onset AF (1–3 days), anticoagulate with IV heparin for at least 12–24 hours and, if possible, exclude intra-cardiac thrombus with a trans-oesophageal ECHO prior to DC shock. If there is thrombus, anticoagulate with warfarin as above. For emergency cardioversion of AF (<24 h), heparinize prior to shock.

The risk of systemic embolism with cardioversion of AF and other tachyarrhythmias is very low, provided there is no ventricular thrombus, since the coordinated atrial activity prevents formation of clot. Routine anticoagulation with warfarin is not necessary but we would recommend heparin before DC shock, as the atria are often rendered mechanically stationary for several hours after shock even though there is coordinated electrical depolarization.

After successful cardioversion, if the patient is on warfarin, continue anticoagulation for at least 3–4 weeks. Consider indefinite anticoagulation if there is intrinsic cardiac disease (e.g. mitral stenosis) or recurrent AF.

DC cardioversion: special situations

Pregnancy

DC shock during pregnancy appears to be safe but should only be considered after careful discussion with the obstetric team. Auscultate the fetal heart before and after cardioversion and, if possible, the fetal ECG should be monitored.

Pacemakers

There is a danger of damage to the pacemaker generator box or the junction at the tip of the pacing wire(s) and endocardium. Position the paddles in the anteroposterior position as this is theoretically safer. Facilities for back-up pacing (external or transvenous) should be available. Check the pacemaker post-cardioversion—both early and late problems have been reported.

Intra-aortic balloon counterpulsation (1)

Indications

- Cardiogenic shock post-MI.
- Acute severe mitral regurgitation.
- Acute VSD.
- Preoperative (ostial left coronary stenosis).
- Weaning from cardiopulmonary bypass.

Rarely

- Treatment of ventricular arrhythmias post-MI.
- Unstable angina (as a bridge to coronary artery bypass graft (CABG)).

Contraindications

- Aortic regurgitation.
- Bleeding diathesis.
- Aortic dissection.
- Severe aorto-iliac atheroma.
- Dilated cardiomyopathy (if patient not a candidate for transplantation).

Complications

- Aortic dissection.
- Thrombocytopenia.
- Arterial perforation.
- Peripheral embolism.
- Limb ischaemia.
- Balloon rupture.

Principle

The device consists of a catheter with a balloon (40 mL size) at its tip, which is positioned in the descending thoracic aorta. The balloon inflation/deflation is synchronized to the ECG. The balloon inflates just after the dicrotic notch (in diastole), thereby increasing pressure in the aortic root and increasing coronary perfusion. The balloon deflates just before ventricular systole, thereby decreasing afterload and improving LV performance (see Fig.18.9).

Counterpulsation has a number of beneficial effects on the circulation:

- increased coronary perfusion in diastole.
- reduced LV end-diastolic pressure.
- reduced myocardial oxygen consumption.
- increased cerebral and peripheral blood flow.

The intra-aortic balloon cannot assist the patient in asystole or VF; it requires a minimum cardiac index of 1.2–1.4 L/min/m², often necessitating additional inotropes.

Balloon insertion

Previous experience is essential. Formerly, a cut-down to the femoral artery was required, but newer balloons come equipped with a sheath, which may be introduced percutaneously. Using fluoroscopy, the balloon is positioned in the descending thoracic aorta with the tip just below the origin of the left subclavian artery. Fully anticoagulate the patient with IV heparin. Some units routinely give IV antibiotics (flucloxacillin) to cover against *Staphylococcus* infection.

Triggering and timing

The balloon pump may be triggered either from the patient's ECG (R wave) or from the arterial pressure waveform. Slide switches on the pump allow precise timing of inflation and deflation during the cardiac cycle. Set the pump to 1:2, to allow you to see the effects of augmentation on alternate beats (see Fig. 18.10).

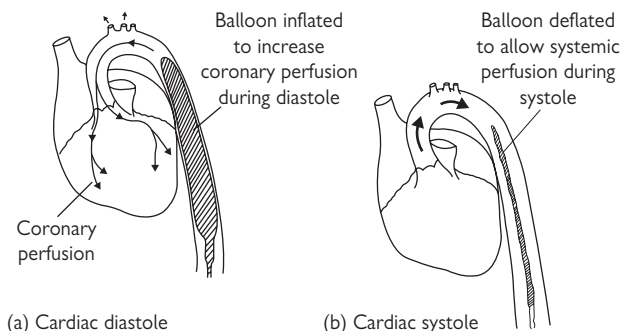


Fig. 18.9 Intra-aortic-balloon counterpulsation. Reproduced with permission from Ramrakha P, Moore K, and Sam M (2010). *Oxford Handbook of Acute Medicine*. 3rd ed. Oxford: Oxford University Press.

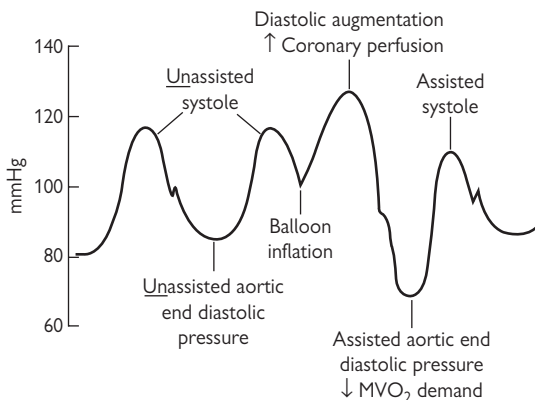


Fig. 18.10 Arterial waveform variations during intra-aortic balloon pump (IABP) therapy. MVO₂ = myocardial oxygen consumption.

IABP removal

- The patient may be progressively weaned by gradually reducing the counterpulsation ratio (1:2, 1:4, 1:8, etc.) and/or reducing the balloon volume and checking that the patient's BP remains stable.
- Stop the heparin infusion and wait for the activated clotting time (ACT) to fall <150 s (activated partial thromboplastin time (aPTT) <1.5 x normal).
- Using a 50 mL syringe, have an assistant apply negative pressure to the balloon.
- Pull the balloon down until it abuts the sheath; do not attempt to pull the balloon into the sheath.
- Withdraw both the balloon and sheath and apply firm pressure on the femoral puncture site for at least 30 minutes or until the bleeding is controlled.

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Intra-aortic balloon counterpulsation (2)

Trouble-shooting

- Seek help from an expert! There is usually an on-call cardiac perfusionist or technician, senior cardiac physician, or surgeon.
- Counterpulsation is inefficient with heart rates over 130/min. Consider anti-arrhythmics or 1:2 augmentation instead.
- Triggering and timing: for ECG triggering, select a lead with the most pronounced R wave; ensure that the pump is set to trigger from the ECG not pressure; permanent pacemakers may interfere with triggering—select a lead with a negative and the smallest pacing artefact. See also Fig. 18.11. Alternatively, set the pump to be triggered from the external pacing device. A good arterial waveform is required for pressure triggering; the timing will vary slightly depending on the location of the arterial line (slightly earlier for radial artery line cf. femoral artery line). Be guided by the haemodynamic effects of balloon inflation and deflation rather than the precise value of the delay.
- Limb ischaemia: this is exacerbated by poor cardiac output, adrenaline, noradrenaline, and peripheral vascular disease. Wean off and remove the balloon.
- Thrombocytopenia: commonly seen; does not require transfusion unless there is overt bleeding, and it returns to normal once the balloon is removed. Consider prostacyclin infusion if the platelet counts fall below $100 \times 10^9/L$.

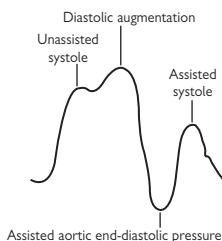
- (a) Inflation of the IAB prior to aortic valve closure

Waveform characteristics:

- Inflation of IAB prior to dirotic notch
- Diastolic augmentation encroaches onto systole (may be unable to distinguish)

Physiologic effects:

- Potential premature closure of aortic valve
- Potential increase in LVEDV and LVEDP or PCWP
- Increased left ventricular wall stress or afterload
- Aortic regurgitation
- Increased MVO_2 demand



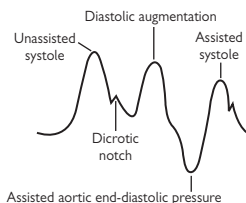
- (b) Inflation of the IAB markedly after closure of the aortic valve

Waveform characteristics:

- Inflation of the IAB after the dirotic notch
- Absence of sharp V
- Suboptimal diastolic augmentation

Physiologic effects:

- Suboptimal coronary artery perfusion



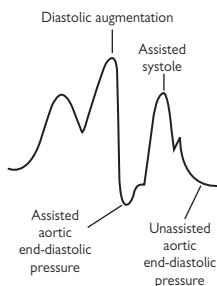
- (c) Premature deflation of the IAB during the diastolic phase

Waveform characteristics:

- Deflation of IAB is seen as a sharp drop following diastolic augmentation
- Suboptimal diastolic augmentation
- Assisted aortic end-diastolic pressure may be equal to or less than the unassisted aortic end-diastolic pressure
- Assisted systolic pressure may rise

Physiologic effects:

- Suboptimal coronary perfusion
- Potential for retrograde coronary and carotid blood flow
- Angina may occur as a result of retrograde coronary blood flow
- Suboptimal afterload reduction
- Increased MVO_2 demand



- (d) Deflation of the IAB as the aortic valve is beginning to open

Waveform characteristics:

- Assisted aortic end-diastolic pressure may be equal to the unassisted aortic end-diastolic pressure
- Rate of rise of assisted systole is prolonged
- Diastolic augmentation may appear widened

Physiologic effects:

- Afterload reduction is essentially absent
- Increased MVO_2 consumption due to the left ventricle ejecting against a greater resistance and a prolonged isovolumetric contraction phase
- IAB may impede left ventricular ejection and increase the afterload

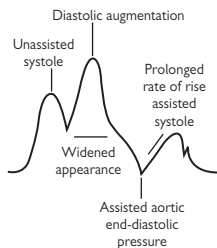


Fig. 18.11 Timing errors. (a) Early inflation; (b) late inflation; (c) early deflation; (d) late deflation. IAB = intra-aortic balloon; LVEDV = left ventricular end-diastolic volume; LVEDP = left ventricular end-diastolic pressure; MVO_2 = myocardial oxygen consumption.

Needlestick injuries

Occupational exposures to bloodborne viruses (BBVs) in healthcare workers can be divided into two groups: percutaneous (needlestick) and mucocutaneous (through broken skin or via splashes into the eyes). High-risk body fluids include: blood, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, amniotic fluid, human breast milk, cerebrospinal fluid, saliva (in dentistry), semen, vaginal secretions, and unfixed tissues and organs, as well as vomit, faeces, and urine when contaminated with blood. The major pathogens associated with needlestick injuries and mucocutaneous exposures are:

- hepatitis B virus (HBV).
- hepatitis C virus (HCV).
- human immunodeficiency virus (HIV).

Occupational exposures to BBVs can be caused by:

- not properly disposing of used needles.
- recapping needles.
- not using protective equipment, e.g. eye protection.

Prevention

Assume that every patient is potentially infected with a blood-borne infection. The same precautions should be taken for every patient and every procedure.

- Cover skin cuts and abrasions with waterproof dressings.
- Never recap needles or pass sharps hand to hand.
- Always dispose of used needles promptly in sharps disposal.
- Never leave sharps to be cleared up by others.
- Use eye protection. Ordinary spectacles offer inadequate protection. Use safety glasses that fit over spectacles.
- Double gloving: in case of needlestick, 80% of the visible blood can be removed by latex in a surgical glove. With double gloving, the inner glove will remove a further 80% of the remaining blood on the needle.

Management of exposure incidents

- If the mouth or eyes are involved, wash thoroughly with water.
- If skin is punctured, let the wound bleed and wash it with soap or chlorhexidine and running water. Avoid scrubbing or sucking.
- Report to the occupational health department to arrange immediate assessment or, if out of hours, attend the emergency department in accordance with the local policy.

Assessment of the risk of BBVs transmission

Estimated seroconversion risks are:

- *hepatitis B*: 30% for percutaneous exposure of a non-immune individual to HBsAg- and HBeAg-positive source.
- *hepatitis C*: 1.9% for percutaneous exposure to HCV-infected blood with detectable HCV RNA.
- *HIV*: 0.3% for percutaneous exposure to HIV-infected blood.

Factors increasing the risk following injury include:

- percutaneous injury is higher risk than mucous membrane or broken skin exposure.
- injury with a device directly from a source patient's artery/vein.
- injury from a hollow-bore and wide-gauge needle.
- deep injury.
- visible blood on the device.
- high HIV viral load, or HBeAg in the source patient.
- staff member inadequately immunized against hepatitis B.

Approaching source patients for BBV testing

- Due to the sensitivity of the issue, the source patient should not be approached by the exposed member of staff.
- Occupational health (or the emergency department if out of hours) will arrange this test in accordance with local policies.

Post-exposure prophylaxis for HIV

Risk assessment and follow-up is carried out by occupational health (emergency department out of hours). If the risk of infection is considered to be significant, post exposure prophylaxis (PEP) should be started, ideally within an hour and certainly within 72h. Most hospitals recommend three agents:

- zidovudine and lamivudine (co-administered as Combivir[®], 1 tablet bd) or tenofovir/emtricitabine.
- a protease inhibitor (e.g. ritonavir-boosted lopinavir).

PEP therapy is associated with significant side-effects. The initial discussion and subsequent follow-up should be with a clinician experienced in the use of these agents. If the 'donor' is known to be HIV positive, ask about their antiretroviral therapy history, as this may alter the choice of drugs. Where possible, the 'donor' in such an injury should be encouraged to test for HIV to allow PEP therapy to be stopped.

Post-exposure prophylaxis for HBV

If the patient has been vaccinated at least twice with HB vaccine, and is known to be a responder (anti-HBs >10 iu/mL), they should be given a booster injection, with a second dose one month later. For patients who have not been vaccinated or are known to be non-responders, they should be given an immediate injection of hepatitis B immunoglobulin (HBIG) and commence an accelerated course of HB vaccination, or have a booster dose if previously immunised.

Post-exposure prophylaxis for HCV

Although there is no vaccine or effective PEP against hepatitis C, evidence suggests that early treatment with high-dose interferon can result in viral clearance in >90% of recently infected individuals. This emphasizes the importance of close and timely follow-up of exposed workers. Therefore, all individuals exposed to HCV should be tested for HCV antibodies at the time of exposure and at 6–12 weeks and 26 weeks.

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Clinical trials

Listed in alphabetical order 832

ABSORB

A BioabsORBable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions trial

Purpose: to assess the efficacy and safety of a bioabsorbable everolimus-eluting stent in 30 patients with single *de novo* coronary artery lesions.

Follow-up: 12 months

Results: procedural success was 100% and the device success 94%. At 12 months the rate of major adverse clinic events was 3.3%, with only one patient having a non-ST elevation infarct and no target lesion revascularization required. No late-stent thrombosis was recorded. These results suggest that bioabsorbable drug-eluting stents are safe.

Reference: Ormiston JA et al. (2008). *Lancet* **371**: 873–4.

ACUITY

Acute Catheterization and Urgent Intervention Triage Strategy trial

Purpose: a large multicentre prospective trial designed to establish the optimal antithrombotic treatment regimens in patients with unstable angina or non-ST elevation myocardial infarction undergoing early percutaneous coronary intervention.

Follow-up: 30 days

Results: bivalirudin monotherapy provided superior outcomes compared with any heparin plus glycoprotein (GP) IIb/IIIa inhibitor regime at 30 days. There was also a significant reduction in major bleeding with bivalirudin monotherapy.

Reference: Stone GW et al. (2006). *N Engl J Med* **355**: 2203–16.

CARE-HF

Cardiac Resynchronization—Heart Failure trial

Purpose: to assess the impact of cardiac resynchronization with biventricular pacing in patients with New York Heart Association (NYHA) class III or IV heart failure receiving optimal medical therapy on mortality and morbidity.

Follow-up: mean 29.4 months

Results: cardiac resynchronization therapy improved mortality in patients with heart failure.

Reference: Cleland J et al. (2005). *N Engl J Med* **352**: 1539–49.

COURAGE

Clinical Outcomes Utilising Revascularisation and Aggressive drug Evaluation trial

Purpose: to evaluate the impact of percutaneous coronary intervention (PCI) on prognosis in patients with stable coronary artery disease, compared with medical therapy.

Follow-up: mean 4.6 years

Results: in patients on optimal medical therapy, an initial strategy of routine PCI does not reduce the risk of death, myocardial infarction (MI), or other cardiovascular (CV) events when compared with a strategy of selective PCI for angina.

Reference: Boden W et al. (2007). *N Engl J Med* **356**: 1503–16.

HORIZONS-AMI

Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial

Purpose: to compare the efficacy of primary percutaneous coronary intervention (PCI) with paclitaxel-eluting (TAXUS) stent versus bare metal stent in patients presenting with ST elevation myocardial infarction.

Follow-up: 1 year

Results: a significantly reduced rate of revascularization with no increase in the rate of stent thrombosis in patients treated with paclitaxel-eluting stents. There was no difference in mortality between treatment arms, demonstrating safety of drug-eluting stenting for primary PCI.

Reference: Stone GW et al. (2009). *N Engl J Med* **360**: 1946–59.

LEADERS

Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization trial

Purpose: to assess the safety and efficacy of a biodegradable biolimus-eluting polymer stent compared with a sirolimus-eluting durable polymer stent. The primary end-point was a composite of cardiac death, MI, and target vessel revascularization.

Follow-up: 9 months

Results: the biodegradable biolimus-eluting stent was non-inferior to sirolimus-eluting stents for the primary end-point at 9 months, suggesting it represents a safe and effective alternative to a durable stent in patients with *de novo* coronary artery lesions.

MIST

Migraine Intervention with Starflex Technology trial

Purpose: a multicentre double-blind sham-controlled trial to evaluate the effectiveness of percutaneous patent foramen ovale (PFO) closure to resolve refractory migraine.

Follow-up: 180 days

Results: there was no difference in resolution of migraine with PFO closure. However, those with PFO closed did report a reduction in the number of headache days experienced.

Reference: Dowson AJ et al. (2008). *Circulation* **117**: 1397–404.

OASIS 5

Fifth Organization to Assess Strategies in Ischemic Syndromes

Purpose: to compare fondaparinux 2.5 mg daily vs. enoxaparin 1 mg/kg of body weight twice daily in patients presenting with acute coronary syndromes. The primary end-point was death, MI, or refractory ischaemia at 9 days. Additionally, major bleeding and longer-term mortality and morbidity at 180 days were evaluated.

Follow-up: 6 months

Results: fondaparinux is non-inferior to enoxaparin in reducing the short-term risk of ischaemic events but it substantially reduced the risk of major bleeding (2.2% vs. 4.1%, $P < 0.001$) and improves long-term mortality and morbidity.

Reference: Yusuf S et al. (2006) *N Engl J Med* **354**: 1464–76.

PARTNER

Placement of Aortic Transcatheter Valve trial

Purpose: multicentre randomized clinical trial to evaluate the impact of transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis considered not to be suitable candidates for conventional surgery. The primary end-point was all-cause mortality.

Follow-up: mean 1.6 years

Results: significant reduction in all-cause mortality after 1 year. There was, however, an increase in the rate of major stroke and vascular complications at 30 days.

Reference: Leon MB et al. (2010). Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* **363**: 1597–607.

PLATO

Platelet inhibition and Patient Outcomes trial

Purpose: to compare outcomes in patients presenting with acute coronary syndrome with or without ST-segment elevation treated with ticagrelor 180 mg loading followed by 90 mg daily dose, vs. clopidogrel 300 mg and 75 mg daily dose. Primary end-points included cardiovascular death, MI, and stroke.

Follow-up: 1 year

Results: patients treated with ticagrelor had lower cardiovascular mortality compared with clopidogrel (9.8% vs. 11.7%, $P<0.001$) but a small, albeit non-significant, increase in major bleeding.

Reference: Wallentin L et al. (2009). *N Engl J Med* **361**: 1045–57.

SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

Purpose: to evaluate whether amiodarone or a single-lead implantable cardiac defibrillator could reduce death in patients with NYHA class II or III heart failure.

Follow-up: median 45.5 months

Results: a single-lead implantable defibrillator reduced mortality by 23% in patients with NYHA class II or III and left ventricular ejection fraction $<35\%$, whereas amiodarone did not influence survival.

Reference: Bardy G et al. (2005). *N Engl J Med* **352**: 225–37.

SPIRIT IV

Clinical evaluation of the XIENCE V[®] everolimus eluting coronary stent system in the treatment of subjects with de novo native coronary artery lesions

Purpose: to compare the efficacy of everolimus-eluting (XIENCE) vs. paclitaxel-eluting (TAXUS) stents in patients undergoing PCI for de novo coronary artery lesions.

Follow-up: 1 year

Results: in patients without diabetes, everolimus-eluting stents reduced the primary end-point of target lesion failure by 54% ($P<0.0001$) and major adverse cardiovascular events by 52% ($P<0.0001$). However, in patients with diabetes, there were no statistically significant differences at 1 year.

Reference: Stone GW et al. (2010). *N Engl J Med* **362**: 1663–74.

TRITON-TIMI 38

Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis In Myocardial Infarction

Purpose: to compare outcomes in patients with moderate–high-risk acute coronary syndromes scheduled to receive PCI, treated with prasugrel 60 mg loading followed by 10 mg daily dose vs. clopidogrel 300 mg loading and 75 mg daily dose.

Follow-up: 15 months

Results: prasugrel was associated with a significantly lower incidence of ischaemic events than clopidogrel. It was particularly effective in specific patient subgroups such as those with diabetes mellitus (30% relative risk reduction). However, it was associated with significantly higher bleeding complications, resulting in no difference in all-cause mortality.

Reference: Antman EM et al. (2008). *J Am Coll Cardiol* **51**: 2028–33.

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