**CARDIVASCULAR PATHOLOGY**

|  |
| --- |
| CONTENT  **Cardiovascular system;**  Review of anatomy and physiology, cardiac failure, cardiomyopathies, myocarditis and pericarditis,  rheumatic fever and rheumatic heart disease, valvular heart disease and infective endocarditis, disorders of arteries,  hypertension, disorders of veins and lymphatics. |

**ANATOMY AND PHYSIOLOGY.** Average weight of the heart in an adult male is 300-350 gm while that of an adult female is 250-300 gm. The heart is divided into four chambers: a right and a left atrium and a right and a left ventricle. The atria are separated by a thin interatrial partition called *interatrial septum*, while the ventricles are separated by thick muscular partition called *interventricular septum.* The thickness of the right ventricular wall is 0.3 to 0.5 cm while that of the left ventricular wall is 1.3 to 1.5 cm. The blood in the heart chambers moves in the prescribed pathway: venous blood from systemic circulation → right atrium → right ventricle →pulmonary arteries →lungs → pulmonary veins → left atrium→ left ventricle → aorta →systemic arterial supply.The transport of blood is regulated by cardiac valves: two atrioventricular valves, tricuspid on the right and mitral (bicuspid) on the left; and two semilunar valves with three leaflets each, the pulmonary and aortic valves, guarding the outflow tracts. Wall of the heart consists of the **myocardium**which is covered externally by thin membrane, the **epicardium**or visceral pericardium, and lined internally by a thin layer, the **endocardium.**

The **myocardium** is the muscle tissue of the heart composed of syncytium of branching and anastomosing, striated muscle fibres. The myocardial fibres are connected to each other by irregular joints called as **intercalated discs**. They represent cell membranes of individual cells which act as tight junctions for free transport of ions and action potentials.

The **conduction system** of the heart located in the myocardium is responsible for regulating rate and rhythm of the heart. It is composed of specialised Purkinje fibres which contain contractile myofilaments and conduct action potentials rapidly. The conduction system consists of 4 major components:

1. The **sinoatrial (SA) node** located in the posterior wall of the right atrium adjacent to the point at which the superior vena cava enters the heart. It is responsible for determining the rate of contraction for all cardiac muscle.( cardiac pacemaker).

2. The **atrioventricular (AV) bundle** conducts the impulse from the SA node to the AV node.

3. The **atrioventricular (AV) node**is located on the top of the interventricular septum and receives impulses from the SA node via AV bundle and transmits them to the bundle of His.

4. The **bundle of His**extends through the interventricular septum and divides into right and left bundle branches to respective ventricular walls. The fibres transmit impulses from the AV node to the ventricular walls.

**MYOCARDIAL BLOOD SUPPLY.** Blood is transported to myocardial cells by the coronary arteries which originate immediately above the aortic semilunar valve. Blood flow to the myocardium occurs during diastole. There are **three major coronary trunks**, each supplying blood to specific segments of the heart **:**

1. The **anterior descending branch of the left coronary artery**

2. The **circumflex branch of the left coronary artery**

3. The **right coronary artery**

**HEART FAILURE/ CARDIAC FAILURE**

**Definition**

**Heart failure** is defined as the pathophysiologic state in which impaired functional and structural disorder of the heart results in inadequate maintenance of circulation for metabolic needs of the tissues of the body. CHF is the end-result of various forms of serious heart diseases. It may be **acute**or **chronic.**

The term **congestive heart failure (CHF)** is used for the chronic form of heart failure in which the patient has evidence of congestion of peripheral circulation and lungs.

Heart failure can occur in any age group but primarily affects the elderly. The syndrome of heart failure can be produced by any heart condition that reduces the pumping ability of the heart. HF in elderly persons, diabetic patients, and women may be attributed to diastolic dysfunction.

**CHF** occurs when the heart cannot generate sufficient output to meet the metabolic demands of the tissues- or can only do so at higher than normal filling pressures. The failing heart can no longer efficiently pump the blood delivered to it by the venous circulation. The result is an increased end-diastolic ventricular volume, leading to increased end-diastolic ventricular pressures and eventually elevated venous pressures.

**Etiology**

Heart failure may be caused by one of the following factors, either singly or in combination:

**1. INTRINSIC PUMP FAILURE.** The most common and most important cause of heart failure is **weakening of the ventricular muscle due to disease so that the heart fails to act as an efficient pump.** Most cases of heart failure are due to systolic dysfunction- inadequate myocardial contractile function, a consequence of ischemic heart disease or hypertension. Various diseases which may culminate in pump failure by this mechanisms are as under:

i) Ischaemic heart disease

ii) Myocarditis

iii) Cardiomyopathies

iv) Metabolic disorders e.g. beriberi

v) Disorders of the rhythm e.g. atrial fibrillation and flutter.

**2. INCREASED WORKLOAD ON THE HEART.**

Increased mechanical load on the heart results in increased myocardial demand resulting in myocardial failure. Increased load on the heart may be in the form of pressure load or volume load.

**i) Increased pressure load** may occur in the following states:

a) Systemic and pulmonary arterial hypertension.

b) Valvular disease e.g. mitral stenosis, aortic stenosis, pulmonary stenosis.

c) Chronic lung diseases.

**ii) Increased volume load** occurs when a ventricle is required to eject more than normal volume of the blood resulting in cardiac failure. This is seen in the following conditions:

a) Valvular insufficiency

b) Severe anaemia

c) Thyrotoxicosis

d) Arteriovenous shunts

e) Hypoxia due to lung diseases.

**3. IMPAIRED FILLING OF CARDIAC CHAMBERS.**

Decreased cardiac output and cardiac failure may result from extra-cardiac causes or defect in filling of the heart. Heart failure can also result from diastolic dysfunction – inability of the heart to adequately relax and fill such as:

a) Cardiac tamponade e.g. haemopericardium, hydropericardium

b) Constrictive pericarditis, myocardial fibrosis c) Massive left ventricular hypertrophy

**Types of Heart Failure**

Heart failure may be acute or chronic, right-sided or left-sided, and forward or backward failure.

**ACUTE AND CHRONIC HEART FAILURE.**

Sudden and rapid development of heart failure occurs in the following conditions:

i) Larger myocardial infarction

ii) Valve rupture

iii) Cardiac tamponade

iv) Massive pulmonary embolism

v) Acute viral myocarditis

vi) Acute bacterial toxaemia.

In acute heart failure, there is sudden reduction in cardiac output resulting in systemic hypotension but oedema does not occur. Instead, a state of cardiogenic shock and cerebral hypoxia develops.

**Chronic heart failure.** Develops slowly as observed in the following states:

i) Myocardial ischaemia from atherosclerotic coronary artery disease

ii) Multivalvular heart disease

iii) Systemic arterial hypertension

iv) Chronic lung diseases resulting in hypoxia and pulmonary arterial hypertension

v) Progression of acute into chronic failure.

In chronic heart failure, compensatory mechanisms like tachycardia, cardiac dilatation and cardiac hypertrophy try to make adjustments so as to maintain adequate cardiac output. This results in well-maintained arterial pressure and accumulation of oedema.

**LEFT-SIDED AND RIGHT-SIDED HEART FAILURE.**

The heart as an organ eventually fails as a whole, but functionally, the left and right heart act as independent units. The clinical manifestations of heart failure result from accumulation of excess fluid *upstream* to the left or right cardiac chamber whichever is initially affected.

**Left-sided heart failure.** It is initiated by stress to the left heart. The major causes are as follows:

i) Systemic hypertension

ii) Mitral or aortic valve disease (stenosis)

iii) Ischaemic heart disease

iv) Myocardial diseases e.g. cardiomyopathies, myocarditis.

v) Restrictive pericarditis.

The clinical manifestations of left-sided heart failure result from decreased left ventricular output and accumulation of fluid **upstream**in the lungs. The major pathologic changes are:

i) Pulmonary congestion and oedema causes dyspnoea and orthopnoea .

**Dyspnea** (breathlessness) is the earliest and most significant complaint of patients in left-sided heart failure; cough due to fluid transudation into airspaces. With further cardiac impairment, patients develop dyspnea when recumbent (***orthopnea*)**; this occurs because of increased venous return from the lower extremities and by elevation of the diaphragm when in the supine position. Orthopnea is relieved by sitting or standing, so that such patients usually sleep while sitting upright. **Paroxysmal nocturnal dyspnea** is breathlessness awakening patients from sleep with attacks of extreme dyspnea bordering on suffocation.

ii) Decreased left ventricular output causing hypoperfusion and diminished oxygenation of tissues e.g. in kidneys causing ischaemic acute tubular necrosis, in brain causing hypoxic encephalopathy, and in skeletal muscles causing muscular weakness.

iii) Other manifestations of left ventricular failure include an enlarged heart (cardiomegaly), tachycardia, a third heart sound (S3), and fine rales at the lung bases, produced by respirations through edematous pulmonary alveoli. With progressive ventricular dilation, the papillary muscles are displaced laterally, causing mitral regurgitation and a systolic murmur. Subsequent chronic dilation of the left atrium is often associated with **atrial fibrillation,** manifested by an "irregularly irregular" heartbeat. Such uncoordinated atrial contraction can cause stasis. The stagnant blood is prone to thrombi formation.

|  |
| --- |
| **Right-sided heart failure** occurs as a consequence of left-sided heart failure. Any pressure increase in the pulmonary circulation inevitably produces an increased burden on the right side of the heart. Isolated right-sided heart failure is less common and it occurs in patients with intrinsic disease of lung parenchyma that result in chronic pulmonary hypertension (cor pulmonale). |

|  |
| --- |
|  |

|  |
| --- |
|  |

Conditions affecting the right ventricle primarily, producing right-sided heart failure:

i) As a consequence of left ventricular failure.

ii) Cor pulmonale in which right heart failure occurs due to intrinsic lung diseases

iii) Pulmonary or tricuspid valvular disease.

iv) Pulmonary hypertension secondary to pulmonary thromboembolism.

v) Myocardial disease affecting right heart.

vi) Congenital heart disease with left-to-right shunt.

The clinical manifestations of right-sided heart failure are **upstream**of the right heart such as systemic and portal venous congestion, and reduced cardiac output. The pathologic changes include:

i) Systemic venous congestion in different tissues and organs e.g. subcutaneous oedema on dependent parts, passive congestion of the liver, spleen, and kidneys, ascites, hydrothorax, congestion of leg and neck veins.

ii) Reduced cardiac output resulting in circulatory stagnation causing anoxia, cyanosis and coldness of extremities.

|  |  |  |
| --- | --- | --- |
| |  | | --- | | **Clinical Features** |  |  | | --- | | While the symptoms of left-sided heart failure are due to pulmonary congestion and edema, pure right-sided heart failure causes very few respiratory symptoms. There is systemic and portal venous congestion, with hepatic and splenic enlargement, peripheral edema, pleural effusion, and ascites. As CHF progresses, patients become cyanotic and acidotic, as a result of decreased tissue perfusion. | |

In summary, in early stage the left heart failure manifests with features of pulmonary congestion and decreased left ventricular output, while the right heart failure presents with systemic venous congestion and involvement of the liver and spleen. CHF, however, combines the features of both left and right heart failure.

**BACKWARD AND FORWARD HEART FAILURE.** The mechanism of clinical manifestations resulting from heart failure can be explained on the basis of interdependent backward and forward failure. Inadequate cardiac output called **forward failure** is accompanied by increased congestion of the venous circulation- that is **backward failure.** Eventually other organs are affected by combination of forward and backward failure.

**Backward heart failure-** Either of the ventricles fails to eject blood normally, resulting in rise of end-diastolic volume in the ventricle and increase in volume and pressure in the atrium which is transmitted ***backward***producing elevated pressure in the veins.

**Forward heart failure-** Clinical manifestations result directly from failure of the heart to pump blood causing diminished flow of blood to the tissues, especially diminished renal perfusion and activation of reninangiotensin- aldosterone system.

|  |  |
| --- | --- |
| Right-sided heart failure leads to elevated pressure in the portal vein and its tributaries. Congestion produces an enlarged spleen (**congestive splenomegaly**). Accumulations of transudate in the peritoneal cavity can cause **ascites.**  **Pleural and Pericardial Spaces.** pulmonary edema indicates left-sided heart failure, pleural effusions accompany both right-sided and left-sided heart failure. Pleural effusions (typically serous) can range from 100 mL to well over 1 L and can cause **atelectasis** of the affected lung. Unlike inflammatory edema, the edema fluid (effusion) has a low protein content and lack inflammatory cells.  **Subcutaneous Tissues.** Peripheral edema of dependent portion of the body -ankle (pedal) and pretibial edema is a feature of right heart failure. In severe cases generalized massive edema (anasarca) may be seen.  **COMPENSATORY MECHANISMS: CARDIAC HYPERTROPHY AND DILATATION**  American Heart Association (AHA) guidelines have incorporated a classification system of heart failure that includes four stages. This staging system recognizes that there are established risk factors and structural abnormalities that are characteristic of the four stages of heart failure:  In order to maintain normal cardiac output, several compensatory mechanisms play a role as under:  Compensatory enlargement in the form of i)**cardiac hypertrophy, ii)cardiac dilatation, or both.**  **iii)Tachycardia**  due to **activation of neurohumoral systems. (**Release of the neurotransmitter norepinephrine by the autonomic nervous system increases heart rate and augments myocardia contractility, and vascular resistance. Activation of the renin-angiotensin-aldosterone system increases sodium and water retention – increasing the circulatory volume and increases vascular tone).  **iv)Myocardial structural changes.** Cardiac myocytes adapt to increased workloads by assembling increased number of sarcomeres, enlarging the myocyte (hypertrophy).  According to **The Frank-Starling’s law**on pathophysiology of the heart, the failing dilated heart, in order to maintain cardiac performance, increases the myocardial contractility and thereby attempts to maintain stroke volume. This is achieved by increasing the length of sarcomeres in a dilated heart. In **The Frank -Starling mechanism** the increased end-diastolic filling volumes dilate the heart and cause increased cardiac myofiber stretching; which contract more forcibly, thereby increased cardiac output. If the dilated ventricle is able to maintain cardiac output by this means, the patient is said to be in c**ompensated heat failure.** With time the failing muscle is no longer able to propel sufficient blood to meet the needs of the body; the patient develops **decompensated heart failure.**  Ultimately, dilatation decreases the force of contraction and leads to residual volume in the cardiac chambers causing volume overload resulting in cardiac failure that ends in death **(Fig. 16.4).**   |  | | --- | |  | |

****

**i. Cardiac Hypertrophy**

Is defined as an increase in size and weight of the myocardium. It results from increased pressure load while increased volume load (e.g. valvular incompetence) results in hypertrophy with dilatation of the affected chamber due to regurgitation of the blood through incompetent valve. Stretching of myocardial fibres in response to stress induces the cells to increase in length.

**CAUSES.** Hypertrophy with or without dilatation may involve the left or the right heart, or both sides.

**Left ventricular hypertrophy.** The common causes are as under:

i) Systemic hypertension

ii) Aortic stenosis and insufficiency

iii) Mitral insufficiency

iv) Coarctation of the aorta

v) Occlusive coronary artery disease

vi) Congenital anomalies like septal defects and patent ductus arteriosus

vii) Conditions with increased cardiac output e.g. thyrotoxicosis, anaemia, arteriovenous fistulae.

**Right ventricular hypertrophy.** Mostly due to pulmonary arterial hypertension:

i) Pulmonary stenosis and insufficiency

ii) Tricuspid insufficiency

iii) Mitral stenosis and/or insufficiency

iv) Chronic lung diseases e.g. chronic emphysema, bronchiectasis, pneumoconiosis, pulmonary vascular disease etc.

v) Left ventricular hypertrophy and failure of the left ventricle.

**ii.Cardiac Dilatation**

Hypertrophy of the heart is accompanied by cardiac dilatation. Stress leading to accumulation of excessive volume of blood in a chamber of the heart causes increase in length of myocardial fibres and hence cardiac dilatation as a compensatory mechanism.

**CAUSES.** Accumulation of excessive blood volume of blood within the cardiac chambers from the following causes may result in dilatation of the respective ventricles or both:

i) Valvular insufficiency (mitral and/or aortic insufficiency in left ventricular dilatation, tricuspid and/or pulmonary insufficiency in right ventricular dilatation)

ii) Left-to-right shunts e.g. in VSD

iii) Conditions with high cardiac output e.g. thyrotoxicosis, arteriovenous shunt

iv) Myocardial diseases e.g. cardiomyopathies, myocarditis

v) Systemic hypertension.

***MORPHOLOGIC FEATURES.*** Hypertrophy of the myocardium without dilatation is referred to as **concentric***,* and when associated with dilatation is called **eccentric.**

**(Fig. 16.5).**

****

**A.Concentric cardiac hypertrophy.** Weight of the heart is increased. The chambers show concentric thickening of left ventricular wall (white arrow) with obliterated lumen (hypertrophy without dilatation). **B. Eccentric cardiac hypertrophy.** The heart is heavier. The left ventricular wall is thickened (black arrow) while the lumen is dilated (white arrow) (hypertrophy with dilatation). The weight of the heart is increased above normal, over 500 gm.

***Grossly,*** Thickness of the left ventricular wall is above 15 mm is indicative of significant hypertrophy. In concentric hypertrophy, the lumen of the chamber is smaller than usual, while in eccentric hypertrophy the lumen is dilated.

***Microscopically,*** there is increase in size of individual muscle fibres, degenerative changes and necrosis in the hypertrophied myocardium. Ventricular hypertrophy renders the inner part of the myocardium more liable to ischaemia.

**CARDIOMYOPATHY**

Most cardiac muscle diseases are secondary to some other condition, e.g coronary atherosclerosis, hypertension, or valvular heart disease. However there are also cardiac diseases attributable to **intrinsic myocardial dysfunction**. Such diseases are termed cardiomyopathies (heart muscle diseases).

**a) primary cardiomyopathy**; confined to the myocardium, and **b)** **secondary cardiomyopathy**presenting as the cardiac manifestation of a systemic disorder i.e. myocardial disease with known underlying cause. Cardiomyopathies includes inflammatory disorders e.g myocarditis, immunological diseases e.g. muscular dystrophies, and genetic disorders of the myocardial fibers.

Classification of primary cardiomyopathy and its subtypes is presented in **Table 16.10.**

**A. PRIMARY CARDIOMYOPATHY**

This is a group of myocardial diseases of unknown cause. It is subdivided into the following 3 pathophysiologic categories **(Fig. 16.33):**

****

1. Idiopathic dilated (congestive) cardiomyopathy.

2. Idiopathic hypertrophic cardiomyopathy.

3. Idiopathic restrictive or obliterative or infiltrative cardiomyopathy.

**1.Idiopathic Dilated (Congestive) Cardiomyopathy**

Characterised by gradual progressive cardiac failure along with dilatation of all the four chambers of the heart. The condition occurs often in adults and the average survival from onset to death is less than 5 years. Though the etiology is unknown, a few hypotheses based on associations with the following conditions have been proposed:

i) Possible association of viral myocarditis(especially coxsackievirus B) with dilated cardiomyopathy, due to presence of viral nucleic acids in the myocardium.

ii) Association with toxic damagefrom cobalt and chemotherapy with doxorubicin .

iii) Inherited mutationshave been implicated. Mutations in certain sarcomere proteins such as cardiac troponin-T and I, β-and α-myosin, and α-cardiac actin have been observed causing contractile dysfunction.

iv) Chronic alcoholismhas been found associated with dilated cardiomyopathy. It may be due to thiamine deficiency induced by alcohol and resulting in beri-beri heart disease.

v) Peripartum associationhas been observed. Poorly-nourished women may develop this form of cardiomyopathy within a month before or after delivery (peripartum cardiomyopathy).

***MORPHOLOGIC FEATURES. Grossly,*** the heart is enlarged and increased in weight (up to 1000 gm). The most characteristic feature is prominent dilatation of all the four chambers giving the heart the globular appearance. The cardiac valves are normal.

**Microscopically**. There may be hypertrophy of some myocardial fibres and atrophy of others.

**2.Idiopathic Hypertrophic Cardiomyopathy**

The disease occurs fbetween the age of 25 and 50 years. It is asymptomatic but becomes symptomatic due to heavy physical activity causing dyspnoea, angina, congestive heart failure and even sudden death. Though idiopathic, following factors have been implicated:

i) Autosomal dominant inheritanceof the disease suggesting genetic factors in its causation.

ii) Inherited mutationsin genes encoding for sarcomere proteins in a number of cases of hypertrophic cardiomyopathy i.e.mutations in heavy and light chains of cardiac β-myosin, troponin-I and troponin-T. and compensatory hypertrophy.

iii) Other contributory factorsare: increased circulating level of catecholamines, myocardial ischaemia as a result of thickened vasculature of the myocardium and increased fibrous tissue in the myocardium due to hypertrophy.

***MORPHOLOGIC FEATURES. Gross,:*** cardiac enlargement, increase in weight, normal or small ventricular cavities and myocardial hypertrophy. The hypertrophy of the myocardium is asymmetrical and affects the interventricular septum more than the free walls of the ventricles**.**

***Microscopically,*** the classical feature is the myocardial cell disorganisation in the ventricular septum. Iindividual muscle cells show hypertrophy and large prominent nuclei.

**3.Idiopathic Restrictive (Obliterative or Infiltrative) Cardiomyopathy**

Characterised by restriction in ventricular filling due to reduction in the volume of the ventricles. Restrictive cardiomyopathy includes the following:

i) Cardiac amyloidosis

ii) Endocardial fibroelastosis

iii) Endomyocardial fibrosis

iv) Löeffler’s endocarditis (Fibroplastic parietal endocarditis with peripheral blood eosinophilia)

**B. SECONDARY CARDIOMYOPATHY**

This is a group of myocardial diseases of known etiologies or having clinical associations. This, however, excludes well defined entities such as ischaemic, hypertensive, valvular, pericardial, congenital and inflammatory involvements of the heart. These include:

1. *Nutritional disorders e.g.* chronic alcoholism, thiamine deficiency causing beri-beri heart disease.

2. *Toxic chemicals e.g*. arsenic, lithium and hydrocarbons.

3. *Drugs* e.g. cyclophosphamide, catecholamines.

4. *Metabolic diseases e.g.* haemochromatosis, hypo-and hyperthyroidism.

5. *Neuromuscular diseases e.g.* Friedreich’s ataxia, muscular dystrophies.

6. *Infiltrations* e.g. from leukaemia and carcinoma.

7. *Connective tissue diseases e.g.* rheumatoid arthritis, lupus erythematosus.

**MYOCARDIAL DISEASE**

Involvement of the myocardium occurs in three major forms of diseases ( discussed ahead)—ischaemic heart disease, hypertensive heart disease and rheumatic heart disease. In addition, there are two other broad groups of isolated myocardial diseases:

I. **Myocarditis** i.e. inflammatory involvement of the myocardium; and

****II. **Cardiomyopathy**i.e. a non-inflammatory myocardial involvement with unknown (primary) or known (secondary) etiology.

**MYOCARDITIS**

Inflammation of the heart muscle is called myocarditis.

**Etiologic classification of myocarditis (Table 16.9).**

Myocarditis is divided into 4 main etiologic types described below.

**I. INFECTIVE MYOCARDITIS**

Infectious agents such as bacteria, viruses, protozoa, parasites, fungi, rickettsiae and spirochaetes may cause myocarditis by direct invasion or by their toxins. Some of the common forms include:

**1. Viral myocarditis.**  Some examples are influenza, poliomyelitis, hepatitis, smallpox, chickenpox, measles, mumps, rubella, viral pneumonias, coxsackievirus and HIV infections. Cardiac involvement occurs in about 5% of viral infections.

The damage to the myocardium is caused either by direct viral cytotoxicity or by cell-mediated immune reaction.

***Grossly,*** the myocardium is pale and flabby with dilatation of the chambers with focal or patchy areas of necrosis.

***Histologically,***Initially, there is oedema and infiltration of the interstitial tissue by neutrophils and lymphocytes. Later, there is necrosis of individual myocardial fibres.

**2. Suppurative myocarditis.** Pyogenic bacteria, *Staphylococcus aureus* or *Streptococcus pyogenes*, which cause septicaemia and pyaemia may produce suppurative myocarditis.

***Grossly:-***abscesses in the myocardium or diffuse myocardial involvement.

***Microscopically,*** the exudate chiefly consists of neutrophils, admixed with lymphocytes, plasma cells and macrophages.

**3. Toxic myocarditis.** A number of acute bacterial infections produce myocarditis by toxins e.g. in diphtheria, typhoid fever and pneumococcal pneumonia.

***Grossly,*** similar to that seen in viral myocarditis.

***Histologically,*** small foci of coagulative necrosis in the muscle surrounded by nonspecific acute and chronic inflammatory infiltrate. Toxic myocarditis manifests clinically by cardiac arrhythmias or acute cardiac failure due to involvement of the conduction system.

**4. Infective granulomatous myocarditis.**

Tuberculosis, brucellosis are some examples of bacterial infections characterised by granulomatous inflammation in the myocardium. Tuberculous myocarditis occurs either by haematogenous spread or by extension from tuberculous pericarditis.

**5. Syphilitic myocarditis.** Occur in 2 forms—a *gummatous lesion* consisting of granulomatous inflammation and a *primary non-specific myocarditis* which is rare. The syphilitic gummas in the myocardium may be single or multiple. The gummas may affect the conduction system of the heart.

**6. Protozoal myocarditis.** Chagas’ disease and toxoplasmosis are the two protozoal diseases causing myocarditis. Chagas’ disease caused by *Trypanosoma cruzi* attacks myocardium besides involving the skeletal muscle and the central nervous system. Toxoplasmosis caused by intracellular protozoan, *Toxoplasma gondii.*.

***Microscopically,*** focal degeneration and necrosis of the myocardium, oedema and cellular infiltrate consisting of histiocytes, plasma cells, lymphocytes and polymorphs.

**7. Helminthic myocarditis.** *Echinococcus granulosus a*nd *Trichinella spiralis* are the two intestinal helminths which may cause myocarditis. *Echinococcus* rarely produces hydatid cyst in the myocardium while the larvae of *Trichinella* in trichinosis cause heavy inflammation in the myocardium as well as in the interstitial tissue.

**8. Fungal myocarditis.** Patients with immunodeficiency, cancer and other chronic debilitating diseases are more prone to develop fungal myocarditis. These include: candidiasis, aspergillosis, actinomyosis, cryptococcosis .

**II. IDIOPATHIC (FIEDLER’S) MYOCARDITIS**

Is an isolated myocarditis unaccompanied by inflammatory changes in the endocardium or pericardium and occurs without apparent causes. The condition is rapidly progressive and causes sudden severe cardiac failure or sudden death.***Grossly,*** the heart is soft and flabby. The cardiac chambers are dilated and show hypertrophy. ***Histologically,*** two forms: diffuse type and giant cell (idiopathic granulomatous) type.

**i) Diffuse type** is more common. It is characterised by diffuse non-specific inflammatory infiltrate consisting of lymphocytes, plasma cells, macrophages, eosinophils and polymorphs in the interstitial tissue without formation of granulomas. Late stage shows healing by fibrosis.

**ii) Giant cell type or idiopathic granulomatous type** is characterised by formation of non-caseating granulomas consisting of macrophages, lymphocytes, plasma cells and multinucleate giant cells.

**III. MYOCARDITIS IN CONNECTIVE TISSUE DISEASES**

Inflammatory involvement of the myocardium occurs in a number of connective tissue diseases such as rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, and dermatomyositis.

**IV. MISCELLANEOUS TYPES OF MYOCARDITIS**

Apart from the above forms of myocarditis, miscellaneous group consists of myocarditis caused by a variety of agents:

**1. Physical agents.** -contusion of the myocardium, heat stroke, cardiac surgery and irradiation can initiate non-specific myocarditis. The features consist of an infiltrate of neutrophils, eosinophils and mononuclear cells and shows contraction-band necrosis of the myocardial fibres.

**2. Chemical agents.** Toxic chemicals such as arsenic, phosphorus and carbon monoxide cause focal areas of degeneration and necrosis of myocardial fibres and nonspecific inflammatory reaction.

**3. Drugs.** Changes similar to those induced by chemical poisons are produced by certain drugs such as sulfonamides, catecholamines and cytotoxic compounds.

**4. Immunologic agents.** Myasthenia gravis, progressive muscular dystrophies initiate a state of autoimmunisation against the myocardium resulting in focal myocardial degeneration and necrosis with secondary inflammatory reaction.

**5. Metabolic derangements.** Uraemia, hypokalaemia and shock are associated with degeneration and necrosis of the myocardial fibres, oedema of the interstitial tissue.

**PERICARDIAL DISEASE**

Diseases of the pericardium are secondary to, or associated with, other cardiac and systemic diseases. They are broadly of 2 types:

I. Pericardial fluid accumulations

II. Pericarditis

**I.PERICARDIAL FLUID ACCUMULATIONS**

Accumulation of fluid in the pericardial sac may be watery or pure blood. Accordingly, it is of 2 types: Hydropericardium (pericardial effusion) and haemopericardium.

****

**A. Hydropericardium (pericardial effusion).**

Accumulation of fluid in the pericardial cavity due to noninflammatory causes is called hydropericardium or pericardial effusion. Normally, the pericardial cavity contains 30 to 50 ml of clear watery fluid. Quantities of fluid (up to 1000 ml) can be accommodated in the pericardial cavity without seriously affecting the cardiac function if the accumulation is slow. But sudden accumulation of a smaller volume (up to 250 ml) may produce deficient diastolic filling of the cardiac chambers (cardiac tamponade)

The various types of effusions and their causes are as follows:

**1. Serous effusions.** This is the most common type occurring in conditions in which there is generalised oedema e.g. in cardiac (in CHF), renal, nutritional and hepatic causes. The serous effusion is clear, watery, straw-coloured with specific gravity less than 1.015 (transudate).

**2. Serosanguineous effusion.** Follows blunt trauma to chest and cardiopulmonary resuscitation.

**3. Chylous effusion.** Milky or chylous fluid accumulates in conditions causing lymphatic obstruction.

**4. Cholesterol effusion.** Characterised by the presence of cholesterol crystals such as in myxoedema.

**B. Haemopericardium:-**Accumulation of pure blood in the pericardial sac . The condition must be distinguished from haemorrhagic pericarditis in which there is escape of small quantities of blood into the pericardial cavity. Massive and sudden bleeding into the sac causes compression of the heart leading to cardiac tamponade. The causes of haemopericardium are as under:

i) Rupture of the heart through a myocardial infarct.

ii) Rupture of dissecting aneurysm.

iii) Bleeding diathesis such as in scurvy, acute leukaemias, thrombocytopenia.

iv) Trauma following cardiopulmonary resuscitation or by laceration of a coronary artery.

**II.PERICARDITIS**

Pericarditis is the inflammation of the pericardial layers and is secondary to diseases in the heart or caused by systemic diseases. Primary or idiopathic pericarditis is rare. Pericarditis is classified into acute and chronic type with subtypes based on the character of the exudate **(Table 16.11).**

**A. ACUTE PERICARDITIS**

Acute bacterial and non-bacterial pericarditis are the most frequent forms of pericarditis. These may have the following subtypes:

**1. Serous pericarditis.** Acute pericarditis may be accompanied by accumulation of serous effusion which differs from transudate of hydropericardium in having increased protein content and higher specific gravity. Causes include:

i) Viral infection e.g. coxsackie A or B viruses, influenza virus, mumps virus.

i) Rheumatic fever.

iii) Rheumatoid arthritis.

iv) Systemic lupus erythematosus.

v) Involvement of the pericardium by malignant tumour in the vicinity e.g. carcinoma lung,mediastinal tumours.

vi) Tuberculous pericarditis in the early stage.

***Microscopically,*** the epicardial and pericardial surfaces show infiltration by some neutrophils, lymphocytes and histiocytes. The fluid resorbs with the resolution of underlying disease.

**2. Fibrinous and serofibrinous pericarditis.**

Is the most common type of pericarditis. The various causes of this type of pericarditis are as follows:

i) Uraemia

ii) Myocardial infarction

iii) Rheumatic fever

iv) Trauma such as in cardiac surgery

v) Acute bacterial infections.

Clinically, these cases manifest by friction rub. In cases with advanced fibrinous exudate, pericarditis heals by organisation and develops fibrous adhesions resulting in adhesive pericarditis.

**3. Purulent or fibrinopurulent pericarditis.**

Caused by pyogenic bacteria (e.g. staphylococci, streptococci and pneumococci) and less frequently by fungi and parasites. The infection may spread to the pericardium by the following routes:

i) Direct extension from neighbouring inflammation e.g. in empyema of the pleural cavity, lobar pneumonia, infective endocarditis.

ii) Haematogenous spread.

iii) Lymphatic permeation.

iv) Direct implantation during cardiac surgery.

**4. Haemorrhagic pericarditis:** The exudate consists of admixture of an inflammatory effusion of one of the following together with blood. The causes are as under:

i) Neoplastic involvement of the pericardium

ii) Haemorrhagic diathesis with effusion

iii) Tuberculosis

iv) Severe acute infections

**B. CHRONIC PERICARDITIS**

Chronic pericarditis is the term used for tuberculous pericarditis and the healed stage of one of the various forms of acute pericarditis already described. This includes: , chronic adhesive pericarditis, chronic constrictive pericarditis, and the pericardial plaques.

**1. Tuberculous pericarditis** is the most frequent form of granulomatous inflammation of the pericardium. Lesions may occur by one of the following mechanisms:

i) Direct extension from an adjacent focus of tuberculosis. ii) By lymphatic spread e.g. from tracheobronchial lymph nodes, chronic pulmonary tuberculosis. The exudate is turbid, caseous or blood- stained. Tubercles are visible on the pericardial surfaces.

***Microscopically,*** tuberculous granulomas with caseation necrosis are seen in the pericardial wall. The lesions heal by fibrosis and calcification resulting in chronic constrictive pericarditis.

**2. Chronic adhesive pericarditis.**  Is the stage of organisation and healing by formation of fibrous adhesions in the pericardium following fibrinous, suppurative or haemorrhagic pericarditis. The process begins by formation of granulation tissue and neovascularization. Fibrous adhesions develop between the parietal and the visceral layers of the pericardium and obliterate the pericardial space

**3. Chronic constrictive pericarditis. C**haracterised by dense fibrous or fibrocalcific thickening of the pericardium resulting in mechanical interference with the function of the heart and reduced cardiac output. The condition results from a longstanding preceding causes, e.g.

i) Tuberculous pericarditis

ii) Purulent pericarditis

iii) Haemopericardium

iv) Acute non-specific and viral pericarditis.

The heart is encased in 0.5 to 1 cm thick and dense collagenous scar which may be calcified. As a result, the heart fails to dilate during diastole. The dense fibrocollagenous tissue may cause narrowing of the openings of the vena cavae, resulting in obstruction to the venous return to the right heart and consequent right heart failure.

**RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE**

**Definition**

Rheumatic fever (RF) is a systemic, post-streptococcal, nonsuppurative inflammatory disease, principally affecting the heart, joints, central nervous system, skin and subcutaneous tissues. The chronic stage of RF involves all the layers of the heart (pancarditis) causing major cardiac sequelae referred to as **rheumatic heart disease (RHD).**

**INCIDENCE**

The disease appears in children between the age of 5 to 15 years when the streptococcal infection is most frequent and intense. Both the sexes are affected equally.

The disease is seen more in poor socioeconomic strata of the society living in damp and overcrowded places which promote interpersonal spread of the streptococcal infection .

**ETIOPATHOGENESIS**

There is preceding throat infection with β-haemolytic streptococci of group A in RF. The mechanism of lesions in the heart, joints and other tissues is not by direct infection but by induction of hypersensitivity or autoimmunity. Thus, there are 2 types of evidences in the etiology and pathogenesis of RF and RHD: the *epidemiologic evidence* and the *immunologic evidence.*

**A. EPIDEMIOLOGIC EVIDENCE.** The concept that RF occurs following infection of the throat and upper respiratory tract with β-haemolytic streptococci of Lancefield group A. These evidences are as under:

1. There is a *history* of infection of the pharynx and upper respiratory tract with this microorganism about 2 to 3 weeks prior to the attack of RF. This period is the latent period required for sensitisation to the bacteria.

2. *Subsequent attacks* of streptococcal infection are associated with exacerbations of RF.

3. A higher incidence of RF has been observed after outbreaks and *epidemics* of streptococcal infection of throat in children from schools

4. Administration of *antibiotics* leads to lowering of the incidence and severity of RF and its recurrences.

5. Patients with RF have *elevated titres* of antibodies to the antigens of β-haemolytic streptococci of group A such as antistreptolysin O (ASO) and S, anti-streptokinase, antistreptohyaluronidase and anti-DNAase B.

6. *Socioeconomic factors* like poverty, poor nutrition, density of population, overcrowding result in higher incidence of RF.

7. *Climate* -The incidence is higher in subtropical and tropical regions with cold, damp climate, near rivers which favour the spread of infection.

8. *Heredity.* Susceptibility to develop RF in families, occurrence in identical twins and in individuals with HLA class II alleles supports the inherited characteristic of the disease.

**B. IMMUNOLOGIC EVIDENCE.** During acute RF the throat contains streptococci, the clinical symptoms of RF appear after a delay of 2-3 weeks and the organisms cannot be grown from the lesions in the target tissues. This has led to the concept that lesions have immune pathogenesis.

A susceptible host, on being encountered with group A streptococcus infection, mounts an autoimmune reaction by formation of autoantibodies against bacteria. These autoantibodies cause damage to tissues due to cross-reactivity between epitopes in the components of bacteria and the host. Streptococcal epitopes present on the bacterial cell wall, cell membrane and the streptococcal M protein, are immunologically identical to human molecules on myosin, keratin, actin, laminin.

This molecular mimicry and cross-reactivity between streptococcal M protein and the human molecules forms the basis of autoimmune damage to human target tissues in RHD i.e. cardiac muscle, valves, joints, skin, neurons etc. Further evidences in support are as under:

1. *Cell wall polysaccharide* of group A streptococcus forms antibodies which are reactive against cardiac valves.

2. *Hyaluronate capsule* of group A streptococcus is identical to human hyaluronate present in joint tissues and thus these tissues are the target of attack.

3. *Membrane antigens* of group A streptococcus react with sarcolemma of smooth and cardiac muscle, dermal fibroblasts and neurons of caudate nucleus.

***MORPHOLOGIC FEATURES***

RF is regarded as an autoimmune focal inflammatory disorder of the connective tissues throughout the body. The *cardiac lesions* of RF in the form of pancarditis, particularly the valvular lesions, are its major manifestations. Supportive connective tissues at other sites like the synovial membrane, periarticular tissue, skin and subcutaneous tissue, arterial wall, lungs, pleura and the CNS are all affected (*extracardiac lesions*).

**A. CARDIAC LESIONS**

The cardiac manifestations of RF are in the form of focal inflammatory involvement of the interstitial tissue of all the three layers of the heart- ***pancarditis.***The pathognomonic feature of pancarditis in RF is the presence of distinctive ***Aschoff nodules***or ***Aschoff bodies.***

**THE ASCHOFF NODULES:** are spheroidal tiny structures, 1-2 mm in size, occurring in the interstitium of the heart in RF. They are found in the vicinity of small blood vessels in the myocardium and endocardium and occasionally in the pericardium and the adventitia of the proximal part of the aorta.

*Evolution* of fully-developed Aschoff bodies involves 3 stages:

**1. Early (exudative or degenerative) stage.** The earliest sign of injury in the heart in RF is apparent by ***about 4th week***of illness. Initially, there is oedema of the connective tissue and increase in acid mucopolysaccharide in the ground substance. This results in separation of the collagen fibres by accumulating ground substance. Eventually, the collagen fibres are fragmented and disintegrated - ***fibrinoid degeneration****.*

**2. Intermediate (proliferative or granulomatous) stage.**

The Aschoff body which is pathognomonic of rheumatic conditions**.** This stage is apparent in **4th to 13th** week of illness. Characterized by proliferation of cells that includes infiltration by lymphocytes (mostly T cells), plasma cells and the characteristic ***cardiac histiocytes (Anitschkow cells*)** at the margin of the lesion. Cardiac histiocytes or Anitschkow cells are present in small numbers in normal heart but their number is increased in the Aschoff bodies; therefore they are not characteristic of RHD.

**3. Late (healing or fibrous) stage.** The stage of healing by fibrosis of the Aschoff nodule occurs in about ***12 to 16 weeks***after the illness. The Anitschkow cells in the nodule become spindle-shaped with diminished cytoplasm.

**RHEUMATIC PANCARDITIS.** Although all the three layers of the heart are affected in RF, the intensity of their involvement is variable.

**1. RHEUMATIC ENDOCARDITIS.** Endocardial lesions of RF may involve the valvular and mural endocardium, causing ***rheumatic valvulitis***and ***mural endocarditis****,* respectively. Rheumatic valvulitis is responsible for the major cardiac manifestations in chronic RHD.

**RHEUMATIC VALVULITIS. *Grossly,*** the valves in **acute RF** show thickening and loss of translucency of the valve leaflets or cusps. This is followed by the formation of characteristic, small (1 to 3 mm in diameter), multiple, warty ***vegetations* or *verrucae,*** along the line of closure of the leaflets and cusps. The vegetations in RF are firmly attached so that they are not likely to get detached to form emboli, unlike the friable vegetations of infective endocarditis.The four heart valves are affected, their frequency and severity of involvement varies: mitral valve alone being the most common site, followed in decreasing order of frequency, by combined mitral and aortic valve.

****The tricuspid and pulmonary valves show infrequent and slight involvement. The higher incidence of vegetations on left side of the heart is because of the greater mechanical stresses on the valves of the left heart, especially along the line of closure of the valve cusps.

The **chronic stage of RHD** is characterised by permanent deformity of one or more valves, especially the mitral (in 98% cases alone or along with other valves) and aortic. The approximate frequency of deformity of various valves is as under:

Mitral alone = 37% cases.

Mitral + aortic = 27% cases.

Mitral + aortic + tricuspid = 22% cases.

Mitral + tricuspid = 11% cases.

Aortic alone = 2%.

Mitral + aortic + tricuspid + pulmonary = less than 1% cases.

**Gross appearance** of chronic healed mitral valve in RHD is characteristically *‘fish mouth’* or *‘button hole’* stenosis. Mitral stenosis and insufficiency are commonly combined in chronic RHD. These healed chronic valvular lesions in RHD occur due to diffuse fibrocollagenous thickening and calcification of the valve cusps.

***Microscopically,*** the inflammatory changes begin in the region of the valve rings and then extend throughout the entire leaflet, whereas vegetations are located on the free margin of the leaflets and cusps.

i) In the **early (acute) stage,** the histological changes are oedema of the valve leaflet, presence of increased number of capillaries and infiltration with lymphocytes, plasma cells, histiocytes and Anitschkow cells.

ii) In the **healed (chronic) stage,** the vegetations have undergone organisation. The valves show diffuse thickening as a result of fibrous tissue with hyalinisation, and calcification.

**2. RHEUMATIC MYOCARDITIS. *Grossly,*** in the *early (acute) stage,* the myocardium, especially of the left ventricle, is soft and flabby. In the *intermediate stage,* the interstitial tissue of the myocardium shows small foci of necrosis. Later, tiny pale foci of the Aschoff bodies may be visible throughout the myocardium.

***Microscopically,*** the most characteristic feature of rheumatic myocarditis is the presence of distinctive Aschoff bodies.

**3. RHEUMATIC PERICARDITIS.** Inflammatory involvement of the pericardium accompanies RHD.

***Grossly,*** the finding is fibrinous pericarditis in which there is loss of normal shiny pericardial surface due to deposition of fibrin on its surface and accumulation of slight amount of fibrinous exudate in the pericardial sac. If fibrinous pericarditis fails to resolve there is formation of adhesions resulting in chronic adhesive pericarditis.

***Microscopically***. Aschoff bodies may be seen which later undergo organisation and fibrosis.

**B. EXTRACARDIAC LESIONS**

Patients of the syndrome of acute rheumatism develop lesions in connective tissue elsewhere in the body, the joints, subcutaneous tissue, arteries, brain and lungs.

**1. POLYARTHRITIS.** Acute and painful inflammation of the synovial membranes of some of the joints, especially the larger joints of the limbs, is seen in about 90% cases of RF in adults. As pain and swelling subside in one joint, others tend to get involved, producing the characteristic *‘****migratory polyarthritis*’** involving two or more joints at a time.

***Histologically,*** The synovial membrane and the periarticular connective tissue show hyperaemia, oedema,neutrophilic infiltration. A serous effusion into the joint cavity is present.

**2. SUBCUTANEOUS NODULES** occur ofen in children than in adult. These nodules are small, ovoid and painless. They are attached to deeper structures like tendons, ligaments, fascia or periosteum and therefore remain unnoticed by the patient. Characteristic locations are extensor surfaces of the wrists, elbows, ankles and knees.

***Histologically,*** the subcutaneous nodules of RF are representative of giant Aschoff bodies of the heart.

**3. ERYTHEMA MARGINATUM.** This non-pruritic erythematous rash is characteristic of RF. Lesions occur mainly on the trunk and proximal parts of the extremities.

**4. RHEUMATIC ARTERITIS** involves the coronary arteries and the aorta but also occurs in arteries of various other organs such as renal, mesenteric and cerebral arteries.

**5. CHOREA MINOR** or Sydenham’s chorea or Saint Vitus’ dance is a delayed manifestation of RF as a result of involvement of the central nervous system. The condition is characterised by disordered and involuntary jerky movements of the trunk and the extremities accompanied by emotional instability. The condition occurs more often in young girls.

***Histologically,*** the lesions are located in the cerebral hemispheres, brainstem and the basal ganglia. They consist of small haemorrhages, oedema and infiltration of lymphocytes.

**6. RHEUMATIC PNEUMONITIS AND PLEURITIS.**

Involvement of the lungs and pleura occurs rarely in RF. Pleuritis is accompanied with serofibrinous pleural effusion, Aschoff bodies are not present.

**CLINICAL FEATURES**

The first attack of acute RF appears 2 to 3 weeks after streptococcal pharyngitis, mostly in children between the age of 5 to 15 years. With subsequent streptococcal pharyngitis. The disease presents with migratory polyarthritis and fever. RF has widespread systemic involvement and no single specific laboratory diagnostic test is available. As per revised WHO criteria (2004) based on ***revised Jones’ criteria***(first described by Dr. TD Jones in 1944, and last revised in 1992), following major and minor criteria are included for diagnosis:

**A. Major criteria:**

1. Carditis

2. Polyarthritis

3. Chorea (Sydenham’s chorea)

4. Erythema marginatum

5. Subcutaneous nodules

**B. Minor criteria:**

1. Fever

2. Arthralgia

3. Previous history of RF

4. Laboratory findings of elevated ESR, raised C-reactive protein, and leucocytosis

5. ECG finding of prolonged PR interval.

**C. Supportive evidence** of preceding group A streptococcal infection include: positive throat culture for group A streptococci, raised titres of streptococcal antibodies (antistreptolysin O and S, antistreptokinase, anti-streptohyaluronidase and anti DNAase B).

**Clinical diagnosis of RF and RHD is made in a case with antecedent laboratory evidence of streptococcal throat infection in the presence of *any two of the major criteria, or occurrence of one major and two minor criteria.***

If the heart is spared in a case of acute RF, the patient may have complete recovery without any sequelae. However, once the heart is involved, it is associated with reactivation and recurrences of the disease. **Myocarditis,** is the most life-threatening due to involvement of the conduction system of the heart and results in serious arrhythmias. The long-term sequelae are the chronic valvular deformities, especially the mitral stenosis are:

1. *Cardiac failure* In young patients, cardiac failure occurs due to the chronic valvular deformities, while in older patients coronary artery disease may be superimposed on old RHD.

2. *Bacterial endocarditis* of both acute and subacute type may supervene due to inadequate use of antibiotics.

3. *Embolism* in RHD originates most from mural thrombi in the left atrium in association with mitral stenosis. The organs most frequently affected are the brain, kidneys, spleen and lungs.

4. *Sudden death* may occur in RHD as a result of ball thrombus in the left atrium.

**NON-RHEUMATIC ENDOCARDITIS**

****Inflammatory involvement of the endocardial layer of the heart is called **endocarditis.** Grouped into *non-infective* and *infective* types **(Table 16.6).**

Most types of endocarditis are characterised by the presence of ‘vegetations’ or ‘verrucae’ which have distinct features.

**A. NON-INFECTIVE**

**2.Atypical verrucous (libman-sacks) endocarditis**

Libman and Sacks, two American physicians, described a form of endocarditis in 1924 that is characterised by sterile endocardial vegetations which are distinguishable from the vegetations of RHD and bacterial endocarditis.

**ETIOPATHOGENESIS.** Characteristic lesions of Libman-Sacks endocarditis are seen in *50%* cases of *acute systemic lupus erythematosus (SLE);* other diseases associated with this form of endocarditis are systemic sclerosis, thrombotic thrombocytopenic purpura (TTP) and other collagen diseases.

***MORPHOLOGIC FEATURES. Grossly,*** characteristic vegetations occur most frequently on the mitral and tricuspid valves. The vegetations are sterile unless superimposed by bacterial endocarditis. Unlike vegetations of RHD, the healed vegetations of Libman-Sacks endocarditis do not produce any significant valvular deformity.

**3.non-bacterial thrombotic (cachectic, marantic) endocarditis;** is an involvement of the heart valves by sterile thrombotic vegetations.

**ETIOPATHOGENESIS.** The following diseases and conditions are frequently associated with their presence:

1. In patients having hypercoagulable state from various etiologies e.g. advanced cancer especially adenocarcinomas, chronic tuberculosis, renal failure and chronic sepsis.

2. Occurrence of these lesions in young and well-nourished patients is explained on the basis of *alternative hypothesis* such as allergy, vitamin C deficiency, deep vein thrombosis, and endocardial trauma (e.g. due to catheter in pulmonary artery and haemodynamic trauma to the valves).

***Microscopically,*** the vegetations in NBTE are composed of fibrin along with entangled RBCs, WBCs and platelets. Vegetations in NBTE are sterile and do not cause tissue destruction

**B.INFECTIVE (BACTERIAL) ENDOCARDITIS**

**Definition.** Is serious infection of the valvular and mural endocardium caused by different forms of microorganisms and is characterised by infected and friable vegetations. A few specific forms of IE are named by the microbial etiologic agent causing them e.g. tubercle bacilli, fungi etc. BE is subdivided into 2 clinical forms:

**1. Acute bacterial endocarditis (ABE)** is fulminant and destructive acute infection of the endocardium by highly virulent bacteria in a previously normal heart .

**2. Subacute bacterial endocarditis (SABE)** is caused by less virulent bacteria in a previously diseased heart and has a gradual downhill course in a period of 6 weeks to a few months to years.

**INCIDENCE.** BE may occur at any age, most cases of ABE as well as SABE occur over 50 years of age. Males are affected more often than females.

**ETIOLOGY.** All cases of BE are caused by *infection with microorganisms* in patients with predisposing factors.

**A. Infective agents.** About 90% cases of BE are caused by streptococci and staphylococci. *In ABE,* the most common causative organisms are virulent strains of staphylococci, chiefly *Staphylococcus aureus.* Others are pneumococci, gonococci, β-streptococci and enterococci. *In SABE,* the commonest causative organisms are the streptococci with low virulence, predominantly *Streptococcus viridans,* which forms part of normal flora of the mouth and pharynx*.*

**B. Predisposing factors.** There are 3 main factors which predispose to the development of both forms of BE:

1. Conditions initiating transient bacteraemia, septicaemia and pyaemia.

2. Underlying heart disease.

3. Impaired host defenses.

1. *Bacteraemia, septicaemia and pyaemia:* Bacteria gain entrance to the bloodstream causing transient and clinically silent bacteraemia Some of the common examples are:

i) Periodontal infections such as trauma from vigorous brushing of teeth, tooth extraction and other dental procedures.

ii) Infections of the genitourinary tract such as in catheterisation, obstetrical procedures including normal delivery and abortions.

iii) Infections of gastrointestinal and biliary tract.

iv) Surgery of the bowel, biliary tract and genitourinarytracts.

v) Skin infections such as boils, carbuncles and abscesses.

vi) Upper and lower respiratory tract infections including bacterial pneumonias.

vii) Intravenous drug abuse.

viii) Cardiac catheterisation and cardiac surgery for implantation of prosthetic valves.

2. *Underlying heart disease:* SABE occurs much more frequently in previously diseased heart valves, whereas the ABE is common in previously normal heart. Amongst the commonly associated underlying heart diseases are the following:

i) Chronic rheumatic valvular disease in about 50% cases.

ii) Congenital heart diseases in about 20% cases.

iii) Others-Syphilitic aortic valve disease, prosthetic heart valves.

3. *Impaired host defenses:* deficiency of complement and defective phagocytic function, predispose to BE.

Following are some of the examples of such conditions:

i) Impaired specific immunity in lymphomas.

ii) Leukaemias.

iii) Cytotoxic therapy for various forms of cancers and transplant patients.

iv) Deficient functions of neutrophils and macrophages.

**PATHOGENESIS.** Bacteria causing BE on entering the bloodstream are implanted on the cardiac valves or mural endocardium because they have surface adhesion molecules which mediate their adherence to injured endocardium.

***MORPHOLOGIC FEATURES.*** The characteristic pathologic feature in both ABE and SABE is the presence of vegetations on the valve cusps or leaflets, and less often, on mural endocardium.

***Grossly,*** the lesions are found on the valves of the left heart, most frequently on the mitral, followed in descending frequency, by the aortic, simultaneous involvement of both mitral and aortic valves, and quite rarely on the valves of the right heart. The vegetations in SABE are often seen on previously diseased valves, whereas the vegetations of ABE are found on previously normal valves. The *vegetations* of BE vary in size and are *friable.* They may appear flat, filiform, fungating or polypoid. The vegetations in ABE are bulkier than those of SABE and are located on previously normal valves, may cause ulceration or perforation of the underlying valve leaflet, or may produce myocardial abscesses.

***Microscopically,*** the vegetations of BE consist of 3 zones

i) The *outer layer or cap* consists of eosinophilic material composed of fibrin and platelets.

ii) Underneath this layer is the *basophilic zone* containing colonies of bacteria. .

iii) The *deeper zone* consists of non-specific inflammatory reaction in the cusp itself.

**COMPLICATIONS AND SEQUELAE.** Most cases of BE present with fever. The acute form of BE is characterised by high grade fever, chills and malaise while the subacute form of the disease has non-specific manifestations like slight fever, fatigue, loss of weight. In the early stage, the lesions are confined to the heart, while subsequent progression of the disease leads to involvement of extra-cardiac organs. Complications and sequelae of BE are divided into cardiac and extracardiac **:**

**A. Cardiac complications.** These include the following:

i) Valvular stenosis or insufficiency

ii) Perforation, rupture, and aneurysm of valve leaflets

iii) Abscesses in the valve ring

iv) Myocardial abscesses

v) Suppurative pericarditis

vi) Cardiac failure from one or more of the foregoing complications.

**B. Extracardiac complications.** Since the vegetations in BE are friable, they tend to get dislodged due to rapid stream of blood and give rise to embolism which is responsible for very common and serious extra-cardiac complications. These are as under:

i) Emboli originating from the ***left side of the heart***and entering the systemic circulation affect organs like the spleen, kidneys, and brain causing infarcts, abscesses and Mycotic aneurysms.

ii) Emboli arising from ***right side of the heart***enter the pulmonary circulation and produce pulmonary abscesses.

iii) *Petechiae* may be seen in the skin and conjunctiva due to either emboli or toxic damage to the capillaries.

iv) In SABE, there are painful, tender nodules on the finger tips of hands and feet called ***Osler’s nodes****,* while in ABE there is appearance of painless, non-tender subcutaneous maculopapular lesions on the pulp of the fingers called ***Janeway’s spots***

v) *Focal necrotising glomerulonephritis* is seen more commonly in SABE than in ABE.

**SPECIFIC TYPES OF INFECTIVE ENDOCARDITIS**

Besides BE, various other microbes may occasionally produce infective endocarditis are named according to the etiologic agent causing it. These include the following:

**1. Tuberculous endocarditis.** Tuberculous endocarditis is described separate from the bacterial endocarditis due to specific granulomatous inflammation found in tuberculosis. It is characterised by presence of tubercles on the valvular as well as mural endocardium and may form tuberculous thromboemboli.

**2. Syphilitic endocarditis.** The endocardial lesions in syphilis. The severest manifestation of cardiovascular syphilis is aortic valvular incompetence.

**3. Fungal endocarditis.** Rarely, endocardium may be infected with fungi such as from *Candida albicans, Histoplasma capsulatum, Aspergillus, Mucor*, cryptococcosis, blastomycosis and actinomycosis. Opportunistic fungal infections like candidiasis and aspergillosis are seen more commonly in patients receiving long-term antibiotic therapy, intravenous drug abusers and after prosthetic valve replacement.

**4. Rickettsial endocarditis.** Another rare cause of endocarditis is from infection with rickettsiae.

**VALVULAR DISEASES AND DEFORMITIES**

Many of them result in cardiac failure. **Rheumatic heart disease** is the most common form of acquired valvular disease. Valves of the left side of the heart are involved much more frequently than those of the right side of the heart. The **mitral valve** is affected most often, followed in descending frequency, by the **aortic valve, and combined mitral and aortic valv**es.

The valvular deformities may be of 2 types: *stenosis and insufficiency:*

**Stenosis** is the term used for failure of a valve to open completely during diastole resulting in obstruction to the forward flow of the blood.

**Insufficiency or incompetence or regurgitation** is the failure of a valve to close completely during systole resulting in back flow or regurgitation of the blood.

Can result from intrinsic disease of the valve cusps e.g. endocarditis or disruption of the supporting structures e.g papillary muscles.

* Valvular disease can involve one valve (the mitral being the most common) or more than one valve. Abnormal blood flow through diseased valves produces abnormal heart sounds called **murmurs,** palpated as **thrills.**
* Murmurs are heard at different locations on the chest walls depending on the valve involved, the nature and timing of the murmur determines the quality and timing of the murmur e.g. harsh systolic or soft diastolic murmur.
* Valvular abnormalities can be congenital or acquired. Causes of acquired valvular disease include the following:

|  |  |
| --- | --- |
| **Mitral Valve disease** | **Aortic Valve Disease** |
| Mitral stenosis | Aortic stenosis |
| Postinflammatory scarring (rheumatic heart disease) | Postinflammatory scarring (rheumatic heart disease),Senile calcific aortic stenosis |
| **Mitral Regurgitation** | **Aortic Regurgitation** |
| Abnormalities of leaflets  Postinflammatory scarring, infective endocarditis, rupture of papillary muscle, dilated cardiomyopathy, | Intrinsic valvular disease, Postinflammatory scarring (rheumatic heart disease), infective endocarditis, aortic disease, syphilitic aortitis |

**MITRAL STENOSIS**

Mitral stenosis occurs in approximately 40% of all patients with RHD. About 70% of the patients are women. The latent period between the rheumatic carditis and development of symptomatic mitral stenosis is about two decades.

**ETIOLOGY.** Mitral stenosis is rheumatic in origin. Less common causes include bacterial endocarditis, Libman- Sacks endocarditis, endocardial fibroelastosis .

***MORPHOLOGIC FEATURES***. The appearance of the mitral valve in stenosis varies according to the extent of involvement, the valve leaflets are diffusely thickened by fibrous tissue and/or calcific deposits, especially towards the closing margin. In less extensive involvement, the bases of the leaflets of mitral valve are mobile while the free margins have puckered and thickened tissue with narrowed orifice; this is called as ***‘purse-string puckering’****.* The more advanced cases have rigid, fixed and immobile diaphragm-like valve leaflets with narrow, slit-like or oval mitral opening, commonly referred to as *‘****button-hole’* or *‘fish-mouth’***mitral orifice

**EFFECTS.** In normal adults, the mitral orifice is about 5 cm. Symptomatic mitral stenosis develops if the valve opening is reduced to 1 cm resulting in significant elevation of left atrial pressure from the normal of 12 mmHg to about 25 mmHg leading to dilatation of the left atrium. The elevated left atrial pressure, in turn, raises pressure in the pulmonary veins and capillaries, reducing the pulmonary function and causing **exertional dyspnoea** which is the chief symptom of mitral stenosis. The effects of mitral stenosis can thus be summarised as under:

1. Dilatation and hypertrophy of the left atrium. 2. Normal-sized or atrophic left ventricle due to reduced inflow of blood.3. Pulmonary hypertension resulting from passive backward transmission of elevated left artial pressure which causes:

i) chronic passive congestion of the lungs;

ii) hypertrophy and dilatation of the right ventricle; and

iii) dilatation of the right atrium when right heart failure supervenes.

**MITRAL INSUFFICIENCY**

Mitral insufficiency is caused by RHD in about 50% of patients but in contrast to mitral stenosis, pure mitral insufficiency occurs more often in men (75%). Subsequently, mitral insufficiency is associated with some degree of mitral stenosis.

**ETIOLOGY.** All the causes of mitral stenosis may produce mitral insufficiency, RHD being the most common cause. In addition, mitral insufficiency may result from noninflammatory calcification of mitral valve annulus (in the elderly). A few other conditions cause mitral insufficiency by dilatation of the mitral ring such as in myocardial infarction, myocarditis and left ventricular failure in hypertension.

***MORPHOLOGIC FEATURES.*** The rheumatic process produces rigidity, deformity and retraction of the valve leaflets and fusion of commissures as well as shortening and fusion of chordae tendineae.

.

**EFFECTS.** The regurgitant mitral orifice produces progressive increase in left ventricular end-diastolic volume as well as pressure since the left ventricle cannot empty completely. This results in rise in left atrial pressure and dilatation. As a consequence of left atrial hypertension, pulmonary hypertension occurs resulting in pulmonary oedema and right heart failure. In symptomatic cases of mitral insufficiency, the major symptoms are related to decreased cardiac output (e.g. fatigue and weakness) and due to pulmonary congestion (e.g. exertional dyspnoea and orthopnoea) The effects of mitral insufficiency may be summarised as under:

1. Dilatation and hypertrophy of the left ventricle.

2. Marked dilatation of the left atrium.

3. Features of pulmonary hypertension such as:

i) chronic passive congestion of the lungs;

ii) hypertrophy and dilatation of the right ventricle; and

iii) dilatation of the right atrium when right heart failure supervenes.

**AORTIC STENOSIS**

Aortic stenosis comprises about one-fourth of all patients with chronic valvular heart disease. About 80% patients of symptomatic aortic stenosis are males. It is of 2 main types: non-calcific and calcific type, the latter being more common.

**1. Non-calcific aortic stenosis.** The most common cause of non-calcific aortic stenosis is chronic RHD. Other causes are congenital valvular and subaortic stenosis and congenitally bicuspid aortic valve.

**2. Calcific aortic stenosis.** Calcific aortic stenosis is more common type. Various causes have been ascribed to it. These include healing by scarring followed by calcification of aortic valve such as in RHD, bacterial endocarditis, *Brucella* endocarditis, Monckeberg’s calcific aortic stenosis, healed congenital malformation and familial hypercholesterolaemic xanthomatosis.

***MORPHOLOGIC FEATURES.*** The aortic cusps show fibrous thickening and calcific nodularity of the closing edges. Calcified nodules are found in the sinuses of Valsalva. In rheumatic aortic stenosis, the commissures are fused and calcified, while in non rheumatic aortic stenosis there is no commissural fusion.

**EFFECTS.** Aortic stenosis becomes symptomatic when the valve orifice is reduced to 1 cm2 from its normal 3 cm2. The major effect of aortic stenosis is obstruction to the outflow resulting in concentric hypertrophy of the left ventricle. Later, when cardiac failure supervenes, there is dilatation as well as hypertrophy of the left ventricle (eccentric hypertrophy). The **three cardinal symptoms**of aortic stenosis are: **exertional dyspnoea, angina pectoris** and **syncope. Exertional** dyspnoea results from elevation of pulmonary capillary pressure. Angina pectoris results from elevation of pulmonary capillary pressure and develops due to increased demand of hypertrophied myocardial mass. Syncope results from accompanying coronary insufficiency.

**AORTIC INSUFFICIENCY**

About three-fourth of all patients with aortic insufficiency are males with some having family history of Marfan’s syndrome.

**ETIOLOGY.** In about 75% of patients, the cause is chronic RHD. Other causes include syphilitic valvulitis, infective endocarditis, congenital subaortic stenosis (congenitally bicuspid aortic valve), traumatic rupture of the valve cusps, dissecting aneurysm. ***MORPHOLOGIC FEATURES.*** The aortic valve cusps are thickened, deformed and shortened and fail to close.

**EFFECTS.** As a result of regurgitant aortic orifice, there is increase of the left ventricular end-diastolic volume. This leads to hypertrophy and dilatation of the left ventricle producing massive cardiac enlargement so that the heart may weigh as much as 1000 gm. Failure of the left ventricle increases the pressure in the left atrium and eventually pulmonary hypertension and right heart failure occurs. The characteristic physical findings in a patient of aortic insufficiency are awareness of the beatings of the heart, pounding in the head with each heartbeat, low diastolic and high pulse pressure, rapidly rising and collapsing water hammer pulse (**Corrigan’s pulse**), booming sound over the femoral artery, and systolic and diastolic murmur heard over the femoral artery when it is lightly compressed (**Durozier’s sign**).

Various acquired valvular diseases that may deform the heart valves are listed below:

1. RHD, the commonest cause

2. Infective endocarditis

3. Non-bacterial thrombotic endocarditis

4. Libman-Sacks endocarditis

5. Syphilitic valvulitis

6. Calcific aortic valve stenosis

7. Calcification of mitral annulus

8. Myxomatous degeneration (floppy valve syndrome)

9. Carcinoid heart disease.