CMS 151 GENERAL PATHOLOGY

SUBJECT AREA: GENERAL PATHOLOGY II

Unit 1: Disorders of Circulation, Fluid & Electrolyte Balance

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LEARNING OUTCOMES

At the end of the module the learner should be able to: -

1. Describe disorders of circulation and fluid balance
2. Describe causes of circulatory disorders and fluid balance
3. Describe the pathophysiology of circulatory disorders and fluid balance
4. Describe the effects of disorders of circulation on body functions and fluid balance
5. Explain the clinical implications of circulatory disturbances and fluid balance

UNIT OUTLINE

1. General Introduction and the Physics of Circulation
2. Mechanisms of Circulatory Disorders, Flow and Congestion
3. Thrombosis and Embolism
4. Ischaemia and Infarction
5. Haemorrhage and Haemostasis
6. Blood Donation and Transfusion
7. Shock
8. Fluid Imbalance- Fluid loss (dehydration) and Fluid retention (Oedema)
9. Electrolyte imbalance

MAIN STUDY QUESTIONS

1. What are the factors influencing blood flow?
2. What are the disorders of circulation?
3. What are the causes of circulatory disorders?
4. How do disorders of circulation affect body function?
5. What are the causes and effects of electrolyte imbalance?

Lesson 1: General Introduction to Circulatory Disorders

Learning Outcomes

At the end of the lesson the learner should be able to:

1) Identify components of the circulatory system
2) Describe functions of the circulatory and components of blood
3) Describe the function of the lymphatic
4) Describe the factors influencing blood flow
5) Explain how the system and pulmonary circulatory systems work

1.0 INTRODUCTION

The health of cells and organs of the body depend heavily on uninterrupted circulation to deliver oxygen and nutrients and to remove waste products as well as normal fluid balance. Hence disturbances in circulation, fluid and electrolyte balance have profound effects on the functioning of the body cells and organs.

The circulatory system is a continuous circuit with **two** major subdivisions of the **systemic circulation** and **the pulmonary circulation.** An estimated 60000 miles of vessels runs throughout the body of an adult serving the trillions of cells.

The heart pumps blood into the arteries under high pressure (120 mmHg for the systemic circulation and 22 mmHg of the pulmonary one) to overcome the resistance in small blood vessels. The cardinal requirements for the normal circulatory function are **normal anatomic structures**, **normal physiologic controls** and **normal composition of blood.**

2.0 COMPONENTS OF THE CIRCULATORY SYSTEM

The circulatory system is divided into two main parts: - **the cardiovascular system** - the heart, blood vessels (arterial system, venous system and capillary network) and blood and **the lymphatic system** consisting of lymph vessels, lymph , lymph nodes, lymphoid organs – spleen, thymus, tonsils

The Heart

The heart is a pumping organ made up of **three layers**: - the internal endocardium, the intermediate myocardium which is a cardiac muscular tissue and the external covering layer the pericardium or the visceral layer of the pericardium. Contraction and relaxation of the heart muscle is coordinated by conduction of electrical impulses across the heart muscle carried out by the network conductive tissue (sino atrial node, atrio-ventricular node and the Purkinje system).

Arteries

Arteries are divided into three types namely: - **elastic or conducting arteries** (large vessels with predominant elastic elements) e.g. the aorta, carotids, subclavian, axillary and iliac arteries, **muscular or distributing arteries** (medium sized vessels with a predominance of muscular elements) and **arterioles** (small vessels that control blood supply to the capillary bed).

The walls of arteries have three layers – the tunica intima – the internal layer lined by an endothelium comprising of squamous cells, tunica media or middle layer – the thickest layer (thickness varies with the character of the artery) and tunica adventitia – the outermost layer with loose connective tissue.

Veins

Veins have a similar structure with the arteries but with some variations in the three layers and they do posses valves.

Capillaries

Capillaries form capillary bed, which is the vascular network that connects the terminal ramifications of the small arterioles and small venules.

3.0 FUNCTIONS OF THE CIRCULATORY SYSTEM

1. Transport of all essential substances for cellular metabolism
   a. Respiratory
      - RBCs transport oxygen to the tissue cells and carbon dioxide from the tissues to the lungs.
      - Nutritive – products of digestion to the liver and tissue cells
      - Excretory - Metabolic wastes, excess water and ions
2. Regulation - Hormones and other regulatory molecules
3. Protection - Clotting mechanism and white blood cells (WBCs) – leucocytes

4.0 BLOOD

Blood is a highly specialized connective tissue consisting of two main portions namely the **cellular portion** (**haematocrit**) and the **fluid portion** (**plasma**). The cellular portion called the **haematocrit** consisting of formed elements (the cells) - **erythrocytes** (red blood cells), **leucocytes** (white blood cells) and **thrombocytes** (platelets). The fluid portion is the pla**s**ma.

The Haematocrit

Haematocrit is the cellular portion of blood, which is approximately 45% of the total blood volume. It determines the viscosity of blood and as such; viscosity of blood increases as the haematocrit rises. The factors the affect the viscosity of blood are the haematocrit and concentration and type of proteins.

The Plasma

Plasma is a straw-coloured liquid consisting of water and dissolved solutes. It has sodium (Na) as the major solute hence its concentration contributes a lot to the total osmolality of plasma. Plasma also contains salts, ions organic molecules – metabolites, hormones, enzymes, antibodies and proteins. Plasma forms part of the extracellular fluid of the body.

Physical Characteristics of Blood

1. Is a viscous fluid composed of cells and plasma
2. 99% of the cells are the red blood cells (RBCs)
3. Plasma and extracellular fluid
4. Intracellular fluid

5.0 THE LYMPHATICS

The lymphatic system is an accessory route through which fluid can flow from the interstitial spaces into the blood. It can carry proteins and particulate matter that can not be absorbed directly into blood capillaries away from the interstitial spaces into the blood. They return proteins into the blood system (very essential function). The lymphatic system consists of lymph channels and lymphatic capillaries.

Lymph Channels

Most tissues have lymph channels except the superficial portions of the skin, central nervous system, endomysin of muscles and bones. They have pre-lymphatic channels. Lymph vessels from the lower part of the body empty into the thoracic duct which joins into the left internal jugular vein/left subclavian vein junction. Lymph from the left side of the head, and neck and parts of the chest region enter the thoracic duct before it empties into the veins. Lymph from the right side of the neck and head, right arm, parts of the right thorax drain into the thoracic duct (smaller than left one) which joins the right subclavian/internal jugular veins junction.

Lymphatic Capillaries

Lymphatic capillaries reabsorb fluid (1/10) and proteins into the circulation. A total of 2 – 3 litres of lymph are transported in a day. Lymphatics reabsorb proteins and nutrients from the GIT and carry bacteria away from tissues to areas where they are destroyed. Lymphatic system is important in controlling ISF protein concentration, volume and pressure.

Lymph Flow

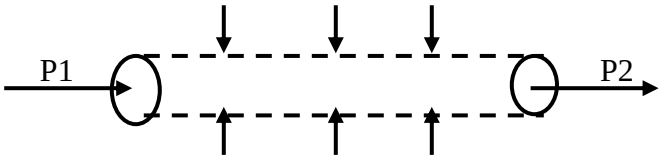
Lymph flow is influenced by interstitial pressure (ISP) and the lymphatic pump. Increased ISF leads to increased lymph flow as seen when there is increased capillary pressure, reduced plasma colloid osmotic pressure, increased interstitial fluid osmotic pressure and increased permeability of the capillaries.

The pumping effect results from contraction of lymph vessels wall, contraction of surrounding skeletal muscles, movement of parts of the body, pulsations of arteries adjacent to the lymph vessels and external compression of tissues.

6.0 THE PHYSICS OF BLOOD FLOW

Blood flow through a vessel is determined by pressure difference across the blood vessel and the vascular resistance

Diagram 1.2: Blood Flow



Resistance (R)

P2 – P1 = $\triangle P$

$Q = \frac{\triangle P}{R}$ ……(i)

$\triangle P = QR$ …… (ii)

$R = \frac{\triangle P}{Q}$ …… (iii)

Where $\triangle P$ - Pressure difference/gradient
Q - Quantity of blood
R - Resistance

Blood flow is the quantity of blood that passes a given point in the circulation in a given time and it is usually 5000 mls/min (5 litres/min) at rest in a normal person (corresponds to the cardiac output).

Blood Pressure

This is the force exerted by the blood against any unit area of the vessel wall. Blood pressure is usually measured in mmHg (1 mmHg is approximately 1.36 cm of water as the density of mercury is 13.6 times that of water). Blood pressure (BP) = Cardiac output (CO) x total peripheral resistance (PR) , BP = CO X PR

Vascular Distensibility

Vascular distensibility = $\frac{\text{Increase in volume}}{\text{Increase in P x Original volume}}$ ……(v)

Vascular compliance = $\frac{\text{Increase in volume}}{\text{Increase in pressure}}$ …… (vi)

Mean Circulatory Pressure

Mean circulatory pressure is a measure of the degree of filling of the circulatory system. It is one of the major factors that determine the rate at which blood flows from the vascular tree into the right atrium of the heart and therefore controls the cardiac output.

7.0 THE SYSTEMIC CIRCULATION

Is also called the greater or peripheral circulation

Functional Parts

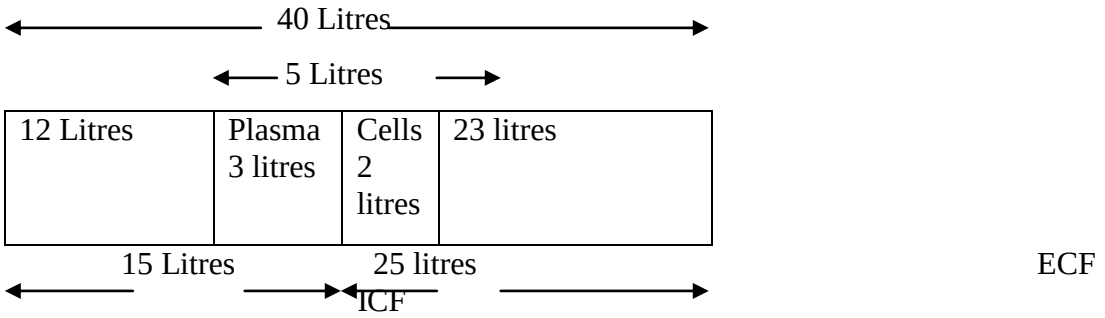
1. Arteries - transport blood under high pressure to the tissues
2. Arterioles - control valves
3. Capillaries - exchange of fluid and nutrients between blood and the interstitial spaces
4. Venules - collect blood from the capillaries and gradually coalese into progressively large veins
5. Veins - conduits for transport of blood from the tissues back to the heart.

Basic Considerations

1. The proper functioning of the heart depends on: -
   a. SAN/AVN and the conducting system
   b. Autonomic nervous system (ANS)
   c. Cardiac muscle
   d. Mechanical soundness of the heart system
2. CO = Stroke volume (SV) x Blood pressure (BP)
3. BP = Cardiac output (CO) x total peripheral resistance (TPR)
4. Pressure gradient for venous return = mean systemic pressure - total peripheral resistance (TPR)
5. Blood consist of RBCs, WBCs, plasma and clotting factors
6. Body fluid comprises of blood, water and Lymph
7. The kidneys maintain the fluid, water and electrolyte balance.

Diagram 1.3: Fluid Distribution in the body

Considered below is the body fluid distribution in an average man of 70 kg weight.



Where ECF is extracellular volume and ICF is intracellular volume.

8.0 THE PULMONARY CIRCULATION

TASKS

1. **In your groups discuss how the circulatory system works**
2. **make a list of new words and explain their meaning**

Lesson 2: Mechanisms of Circulatory Disorders & Blood Flow Disorders

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Describe mechanisms of fluid disturbance
2. Describe the causes and effects of disturbance of blood flow
3. Describe the causes and effects of disturbance of congestion

Mechanisms of Disturbances

1.0 INTRODUCTION

Disorders of circulation which are associated with lesions of the heart and blood vessels involve disturbances of **blood flow and body fluids** and the effects thereof. The disorders encompass processes or situations arising from disturbed functions of the cardiovascular system. Changes occurring in blood composition do influence a great deal of the effects of disturbed circulation. It involves the changes in composition and volume of body fluids as a result of various processes at fault in the cardiovascular system with a resultant disturbance in water and electrolytes.

2.0 MECHANISMS OF CIRCULATORY DISTURBANCE

The disturbances of blood flow (heamodynamic disturbances) occur via two main mechanisms namely 1) Disturbances in the volume of the circulating blood (and distribution) such as **hyperaemia** (increased blood flow), **congestion**, **haemorrhage** and **shock** and 2) Obstruction of blood flow such as **thrombosis, embolism, ischaemia** and **infarction**.

3.0 CHANGES IN BLOOD FLOW

1. Increased blood flow
   a. Total (whole body) – Physiological and Pathological
   b. Local – Physiological and Pathological

2. Decreased blood flow.
   a. Total – Physiological and Pathological
   b. Local - Physiological and Pathological

The factors that influence the changes in blood flow include: -
Blood composition and viscosity

1. Heart rate
2. Metabolic rate
3. Activity
4. Blood pressure
5. Haemoglobin level
6. Hormones – e.g. adrenaline
7. Size of blood vessels

Explain how these factors control blood flow. Give examples and illustrations. Describe the pathophysiology in each case. State clinical situations that you think can contribute to such influence based on cases at the KDH

Hyperaemia (Increased Blood Flow)

1.0 INTRODUCTION

Hyperaemia is *increased volume of blood within* dilated arterial, arteriolar and capillary vessels of an organ or tissue. It is also referred to us active hyperaemia. Hyperaemia can be acute or chronic in nature. The dilatation is effected through sympathetic stimulation effect on blood vessels and release of vaso-active amines. The affected tissue or organ is pink or red in appearance (erythema). Hyperaemia is an active process resulting from enhanced tissues inflow due to arteriolar dilatation e.g. skeletal muscle during exercise or site of inflammation. This results in increased redness due to engorgement of vessels with oxygenated blood. Increased blood flow can be: -

1. Total increased blood flow (Physiological and Pathological)
2. Locally increased blood flow (Physiological and Pathological)

2.0 TOTAL INCREASED BLOOD FLOW

The arteries relax resulting in increased rate of passage of blood from the arterial to the venous compartment. It can be a physiological process or pathological.

Physiological Causes

- Active hyperaemia in skeletal muscles during exercise
- Increased splanchic circulation after a heavy meal

Pathological Causes

a) Hypoxia – reduced oxygen delivered to the tissues
   1. Anaemia (reduced haemoglobin [Hb] concentration) – cardiac output increases in severe anaemia leading to anaemic hypoxia
   2. Abnormal pulmonary function
      i. Arterial blood not fully oxygenated leading to hypoxaemic hypoxia
      ii. Interference with pulmonary ventilation causing asphyxia where there is increased partial pressure of carbon monoxide ($PaCO_2$) and reduced partial pressure of oxygen (PaO_2)
      iii. Congenital abnormalities of the heart and the blood vessels and which leads to the mixing of oxygenated and deoxygenated blood (hypoxaemic hypoxia)
   3. Ischaemic hypoxia resulting from failure of the heart to maintain adequate circulation.

b) Increased metabolic demands
   1. Thyrotoxicosis
   2. Fever
   3. Convalescence after severe injury

c) Extensive hyperaemia e.g. generalized inflammation of the skin

d) Liver failure – leads to accumulation of vasodilators substances that are supposed to be metabolised by the liver

e) Extensive Paget's disease

3.0 LOCALLY INCREASED BLOOD FLOW

The best illustrations are: -

- Hyperaemia in acute inflammation
- Following a temporary obstruction of the circulation e.g. during surgery on a limb.
- Blushing

Think of other examples in the context of physiological and pathological causes of locally increased blood flow

Decreased Blood Flow

1. Total decreased blood flow (Physiological and Pathological)
2. Locally decreased blood flow

1.0 TOTAL DECREASED BLOOD FLOW

a. Acute myocardial infarction
b. Chronic heart failure due to: - myocardial infarction/ischaemic heart disease, coronary heart disease and increased workload on the heart – pressure or volume load due to valve lesions
c. Shock – decreased tissue perfusion
d. General metabolic depression e.g. in hypothyroidism

2.0 LOCALLY DECREASED BLOOD FLOW (ISCHAEMIA)

It is usually due to: -

a. Arterial narrowing due to diseases of the blood vessel walls – Atheroma, Thrombosis
b. Complete obstruction the blood vessels by thrombosis, embolism and ligatures
c. Venous obstruction due to pressure, thrombus, ligatures and disease e.g. phlebitis.

Venous Congestion

1.0 INTRODUCTION

Venous congestion is accumulation of blood in the venous compartment. It is also called passive hyperaemia as it results from dilatation of the veins and venules due to impaired venous drainage causing congestion. Congestion may be acute or chronic. Chronic venous congestion (CVC) is the most common. The affected tissue or organ is bluish in colour due to accumulation of venous blood (cyanosis). Venous congestion follows a situation where the heart fails to expel all the normal amount of blood leading to increased arterial tone by the sympathetic stimulation and the blood accumulates in the veins, as they are readily distensible.

Classification

Two main classes namely systemic (general) venous congestion and localized venous congestion

2.0 SYSTEMIC (GENERAL) VENOUS CONGESTION

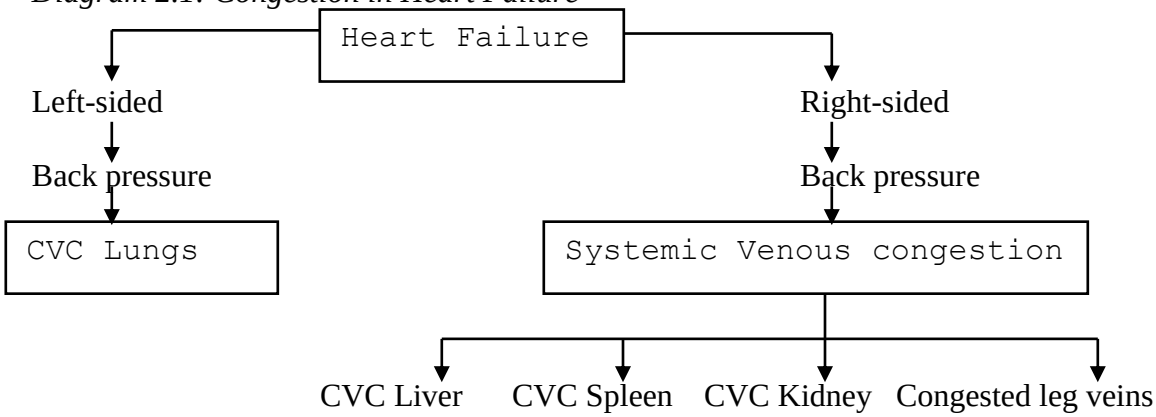
Systemic (general) venous congestion involves engorgement of systemic veins and organs such as the leg veins, liver, spleen, lungs and the kidneys. Systemic venous congestion usually results from right ventricular failure (RVF). Engorgement of systemic veins is easily seen in the neck veins with patient in recumbent position. Congestion of lungs is seen in left-sided heart failure.

Decreased blood flow in the capillaries causes excessive oxygen desaturation leading cyanosis. The congestive element is down played by the ensuring inadequate tissue perfusion and heart failure.

Pathophysiology

- With engorgement, the veins expand to accommodate blood without increasing the venous pressure (VP).
- If the situation persists the venous pressure then increases.
- The neck veins are partially collapsed in standing or sitting positions and do not pulsate because the VP is less than atmospheric pressure, but with increased VP there is pulsation when the blood is approximately at atmospheric pressure.
- Reduced blood flow in heart failure causes a higher degree (more than normal) of oxygen dissociation in the capillaries and in the vascular tissue there is reduction in **haemoglobin** (Hb) leading to purple-blue colour (**cyanosis)** that is seen on the lips and buccal mucosa.
- The sluggishly flowing oxygen deficient blood in engorged veins worsens the cyanosis.

Diagram 2.1: Congestion in Heart Failure



Effects of Venous Congestion

These are the factors that contribute to the clinical features and pathology of venous congestion depending on the organs affected.

1. Reduced blood flow
2. Cyanosis, Oedema
3. Hypoxia
4. Increased venous pressure
5. Increased capillary pressure

Explain the pathophysiology of these effects. Of what clinical relevance will they be? Look for typical examples at the General Hospital.

Structural (Morphological) Changes

These are seen in the liver, spleen, kidneys and the lungs

The Liver

Chronic venous congestion of the liver occurs in right heart failure (commonly) and occlusion of the inferior vena cava ad hepatic vein. The liver is enlarged, tender and palpable.

Macroscopy
- Dark and congested
- Pale with fatty peripheral lobular cells ("Nutmeg appearance")
- "Mottling" due to congestion in the central vein leading to reddish-brown and yellow speaks
- Fibrosis – "cardiac cirrhosis"

Microscopy
- Distended centrilobular veins
- Distended sinusoids
- Atrophy of hepatocytes (liver cells)

The Spleen

Chronic venous congestion of the spleen occurs in right heart failure and portal hypertension. The spleen is enlarged, firm and maintains the firmness and shape on slicing. The red pulp is congested (black appearance). The sinuses in the red pulp are congested. Spleenomegally is marked in portal hypertension.

The Kidneys

Kidneys are slightly enlarged with a dark and congested medulla. Other possible features include presence of RBCs and proteins in urine. Reduced blood flow and tissue hypoxia resulting from the underlying cardiac insufficiency leads to reduced renal perfusion that causes water and salt retention and oedema formation.

3.0 PULMONARY VENOUS CONGESTION

Chronic venous congestion of the lungs occurs in left heart failure. The venules and alveolar capillaries are engorged with blood and pulmonary veins react to the increase in pressure by muscular thickening of the media associated with intimal thickening. The red blood cells (RBCs) escape into the alveoli giving a blood stained sputum.

The alveolar macrophages (which contain haemosiderin) breakdown the RBCs and the released haemosiderin encrust the elastic fibres in the alveoli wall leading to thickening with formation of a firm brown lung – brown indurations. Macrophages accumulate at the alveoli giving a "snow storm appearance".

Chronic congestion of pulmonary veins leads to repeated attacks of pulmonary oedema giving rise to pulmonary hypertension that is associated with the iron laden macrophages (heart failure cells) in the sputum.

4.0 LOCALIZED VENOUS CONGESTION

Localized venous congestion is limited to part of the systemic circulation. This results from mechanical interference with venous drainage usually due to obstruction. Common sites include the spleen, G.I.T and the limbs.

Causes

1. Thrombosis e.g. DVT
2. Pressure e.g. pregnancy
3. Tumour e.g. lymphomas
4. Scarring e.g. liver cirrhosis
5. Ligatures

Effects of local venous congestion

- Local venous congestion can be acute or chronic.
- The effects depend on: - rapidity of development, degree of congestion and duration of congestion
- Local vascular arrangement - anastomosis reduces the effects whereas areas with limited anastomosis show marked effects e.g. the intestines will show: - marked swelling, marked engorgement, haemorrhage and ischaemic necrosis

5.0 CHRONIC VENOUS OBSTRUCTION

- May follow acute venous obstruction
- Occasionally may follow organization of a thrombus, compression by tumours or constriction by fibrous tissue.
- When the obstruction is gradual, collateral veins enlarge and drainage is maintained e.g. in chronic portal venous obstruction of liver cirrhosis, the veins connecting portal venous tributaries with the systemic veins become enlarged and help in drainage.

Effects of Chronic Venous Congestion

1. Oedema
2. In the lungs – dyspnoea and cyanosis
3. Haemorrhage due to damage on blood vessels
4. Cyanotic indurations due to fibrous proliferation of tissues
5. Atrophy due to pressure on the liver, kidney and spleen.
6. Pigmentation due to stasis
7. Fatty change due to reduced oxygen supply.

Lesson 3: Thrombosis and Embolism

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Define basic terms
2. Describe the pathogenesis and pathology of thrombosis
3. Describe the effects of thrombosis
4. Describe the different types of emboli
5. Describe pathogenesis of various types of emboli
6. Describe the pathophysiology and effects of embolism
7. Explain the clinical significance of thrombosis and embolism

Thrombosis

1.0 INTRODUCTION

Thrombosis is the formation of a solid or semi-solid mass called a **thrombus** from constituents of flowing blood within the vascular system during life. A thrombus is a clotted mass forming in the circulation. Haemostatic plugs that are blood clots formed in healthy individuals are the simplest forms of thrombi and thrombosis is a process where there is inappropriate activation of the clotting system. *Blood clotting is a normal protective mechanism but thrombosis is a pathological progression.*

In 1887, Welch defined a *thrombus as a solid mass or plug formed within the heart, arteries, veins or capillaries from the components of the streaming blood*. Thrombosis has a significant impact on the functioning of body tissues/organs/systems in affected individuals.

Clotting

Initiation of a clotting cascade system within the blood leads to thrombin generation hence conversion of soluble plasma protein fibrinogen into insoluble fibrin.

Role of Coagulation system

The coagulation system is involved in both **haemostasis** and **thrombus formation**. Hypercoagubility of blood increases the chances of thrombus formation for example in conditions such as nephrotic syndrome, advanced cancers, extensive trauma, burns and during puerperium. Advancing age, smoking, use of oral contraceptives and obesity catapult these effects. In hypercoagubility states there is an increase in coagulation factors and decreased inhibitors of coagulation.

2.0 PLATELETS, HAEMOSTASIS & THROMBOSIS

Normal platelets in normal numbers are essential if bleeding from a damaged blood vessel is to be brought under control through haemostasis and thrombosis. Thrombosis is an abnormal outcome of a set of normal mechanisms.

Platelet Activities in Thrombus formation

- Platelets adhere to sites of endothelial cell loss or abnormal endothelial cells and release factors which cause platelet aggregation, local formation of fibrin, changes in vessel permeability and stimulation of connective tissue cells
- The microanatomy of the platelets includes the ability to: -
  a) Circulate in plasma in a completely non-active form
  b) Respond rapidly to signals from injured sites of the blood vessel walls (very sensitive to chemical and physical signals).
  c) Contract after adhesion has taken place and release pharmacologically active substances.

3.0 FACTORS PREDISPOSING TO THROMBOSIS

a) Primary (genetic) factors
   a. Deficiency of antithrombin
   b. Deficiency of protein C or S
   c. Defects in fibrinolysis
   d. Mutation in factor V

b) Secondary (acquired) factors
   a. Risk factors
      i. Advanced age
      ii. Prolonged bed rest and immobilization
      iii. Use of oral contraceptives
      iv. Cigarette smoking
      v. Tissue damage e.g. trauma, fractures, burns

   b. Clinical conditions
      i. Heart diseases e.g. myocardial infarction, rheumatic heart disease.
      ii. Atherosclerosis
      iii. Aneurysms
      iv. Varicosities
      v. Disseminated cancers
      vi. Late pregnancy and puerperium

Explain how these factors play role in causation of thrombosis.

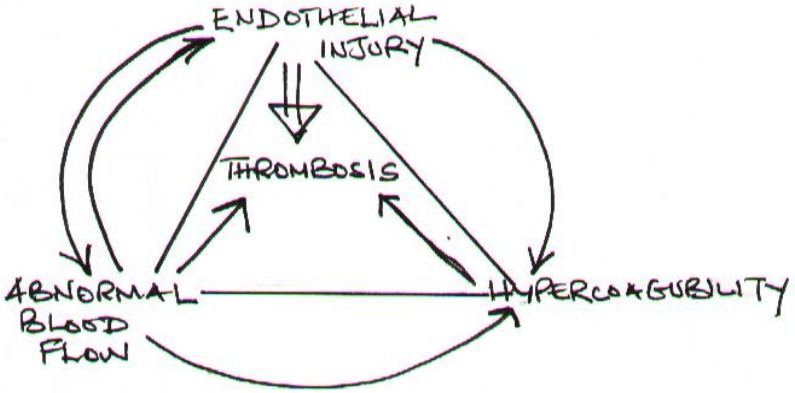
4.0 VIRCHOW'S TRIAD

The process of thrombus formation is characterized by a series of events involving both platelets and coagulation system. There are three main factors that underlie the pathogenesis of thrombosis namely: - The Virchow's triad which comprises of: -

1. ***Alterations of blood flow***
2. ***Alteration to the vessel wall (endothelium)***
3. ***Alteration in composition of the blood***

The factors that promote thrombus formation are contained in the Virchow's Triad (after Rudolf Virchow – the father of modern pathology). Other factors of great significance are the platelets and the blood clotting system.

Diagram 3.1: Virchow's Triad



THE BLOOD VESSEL WALL

The integrity of the blood vessel wall is significant in maintaining normal blood flow. This fate is achieved by the intactness of the vessel endothelium. This is the dominant factor in thrombosis involving the heart or arterial circulation where high flow rates hamper clotting by preventing platelet adhesion or diluting coagulation factors. The endothelium has several functions that enable it carry out its roles.

The functions of the endothelium include: -

1. Protection of flowing blood from thrombogenic substances produced by the subendothelium
2. Enhances anti-thrombotic factors e.g. Heparin-like substances, protein C, tissue plasminogen activator that increases fibrinolytic activity and factors that inhibit platelet aggregation e.g. prostaglandins.

In health the endothelial cells produce vasodilators such as nitric acid, prostacyclin and antithrombin, which prevent formation of a thrombus, and damage to the endothelium allows release of vasoconstrictors and platelet activators e.g. endothelin and von Willibrand factor that lead to activation of the platelets and thrombosis.

Damage to Endothelium of Vessel

Injury to the blood vessels exposes the subendothelial connective tissue e.g. collagen, elastin and von Willebrand which mediate adhesion of platelets and hence play a role in initiating haemostasis and thrombosis. These elements are exposed to the blood platelets triggering the process of platelet activation and adhesion.

Causes of Damage

1. Atherosclerosis
2. Injury to the endocardium -myocardial infarction, cardiac surgery, prosthetic valves, myocarditis
3. Trauma/injury to blood vessels
   a) Burning
   b) Freezing (frost bite)
   c) Haemodynamic stress e.g. in hypertension

   d) Mechanical – e.g. indwelling catheters
   e) Chemical – used in treatment of haemorrhoids and varicose veins, cigarette smoke
   f) Foreign bodies
   g) Surgery
   h) Sutures
4. Inflammation – produces toxins
   a) Heart valves in Rheumatic heart disease and infective endocarditis
   b) Arteries in poly arteritis nodosa and arteritis
   c) Veins - phlebitis
5. Neoplasms - Invasion of small venules by malignant cells
6. Metabolic disorders e.g. diabetes mellitus

ALTERATIONS OF BLOOD FLOW

Normally in the axial flow of blood is a rapid moving stream of leucocytes and red cells while the platelets are found in the slow moving lamina stream adjacent to the central stream. The peripheral stream is made of slow moving plasma that is in contact with the endothelial layer. In blood turbulence or stasis the axial flow pattern is disturbed and platelets come into contact with the endothelium. The changes in flow and stress cause altered endothelial function with enhanced production of agents that promote thrombosis.

The changes that favour thrombus formation are: -
1. Changes in speed of normal lamina flow
2. Loss of lamina pattern and its replacement by a turbulent pattern turbulence of blood)

Reduced Speed of Flow

General or local slowing of blood flow destabilizes the normal axial stream of blood cells allowing white blood cells and platelets to fall out of the main stream and accumulate in the peripheral plasma zone. Stasis of blood can occur in the heart and large vessels e.g. the aorta due to congestive or dilated cardiomyopathy (with dilated heart chambers) and aneurysms (dilated vessels) respectively.

General Reduction

General reduction in speed occurs in severe congestive cardiac failure (CCF) where the circulation time is significantly reduced.

Local Reduction

Commonly occurs in veins of the legs due to prolonged dependence of the limb, reduced muscle pumping activity and proximal occlusion of the venous drainage

Turbulence

Turbulence occurs in areas where arteries branch and narrowed segments of arteries. At these points platelets tend to collect on the outer walls of branches.
In arteries there is rapid flow and any tiny plugs forming will be dislodged but in the veins, blood flow is slow and the presence of valves creates Eddy currents near the valves. Eddy currents do also occur where there is an aneurysm. These currents do slow blood flow.

ALTERATIONS IN BLOOD CONSTITUENTS

This occurs in any situation favouring hypercoagubility of blood for example: -

a) Increased number of platelets (thrombocytosis) and platelet adhesiveness
b) Increased fibrinogen
c) Increased prothrombin
d) Reduced fibrinolytic activity
e) Increased red cell mass (polycythaemia)
f) Increased blood viscosity
g) Abnormalities of thrombosis inhibitors e.g. protein C deficiency, anti-thrombin C deficiency
h) Miscellaneous e.g. oral contraceptives, smoking, some cancers

Platelets

Platelets play a significant role in thrombosis through their concentration within the blood and three mechanisms or ways namely:-

1. Platelet adhesion
2. Platelet aggregation
3. Platelet release reaction (see your notes on cells on inflammation)).

5.0 PATHOGENESIS OF THROMBOSIS

- Damage to the epithelium of the blood vessel exposes the subendothelial connective tissue to the platelets
- Platelets adhere to the site of endothelial injury and release substances such as ADP, 5-hydroxytryptamine (5HT – serotonin), thromboxane, platelet factor 3 and products of prostaglandins.
- Platelet aggregation takes place resulting in liberation of thrombopalstin, which initiates the process of coagulation and fibrin deposition leading to formation of an observable plug called a thrombus.
- In normal life the plug undergoes fibrinolysis if the damage is trivial as fibrinolysis prevents thrombus formation. Hence, if fibrinolysis balances thrombus formation, the plug will not grow and will be overgrown by the endothelium and will eventually resolve.

Diagram 3.2: Pathogenesis of thrombosis

Injury to vessel Change in flow and composition of blood ⟶ Exposure of subendothelium to platelets ⟶ Platelets adhere to exposed surface ⟶ Platelet release reaction ⟶ Platelet aggregation and Activation coagulation system ⟶ Formation of fibrin strands ⟶ Red cells and leucocytes are entangled in fibrin mesh ⟶ Thrombus/clot is formed

6.0 CLASSIFICATION

Appearance and Composition of Thrombi

The appearance of a thrombus is determined by the rate of flow of blood from which it forms. This yields three main appearances: -

1. White (Pale) thrombus
   - Forms in rapidly flowing blood for example in an artery
   - It consists mainly aggregated platelets, some fibrin (fibrin deposition is inversely proportional to the rate of blood flow) and few trapped RBCs
   - It is firm and pale and may vary from grey white to pale red.
   - Example: -Rheumatic endocarditis, Atheroma

2. Red thrombus
   - Forms in stagnant blood in the venous system
   - It is soft, dark red and gelatinous
   - Consists of a meshwork of fibrin strands with entrapped red cells, leucocytes and platelets
   - The fibrin contracts squeezing out fluid leaving a smooth shinny surface.
   - Example: - Deep venous thrombosis (DVT), portal thrombosis in liver cirrhosis

3. Mixed (Laminated) thrombus
   - Many thrombi comprise a mixture of pale and red areas giving a laminated appearance
   - Form in vessels where blood is flowing slowly
   - Consists of alternating layers of platelet aggregates and fibrin network.
   - Example: - in aneurysm

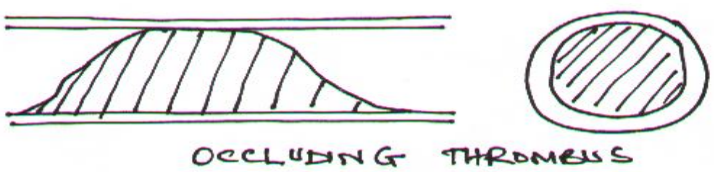
7.0 TYPES OF THROMBI

1. Occluding thrombus
2. Mural thrombus
3. Propagating thrombus

Occlusive thrombi

- New vessels of granulation tissue capillary grow out from the vaso vasorum in the adventitia across the media into and across the intima into the thrombus.
- The thrombotic material is removed by macrophages.
- Thrombus may be replaced by a solid plug of collagenous tissue creating a chance for re-establishment of blood flow.

Diagram 3.3: Occlusive Thrombi

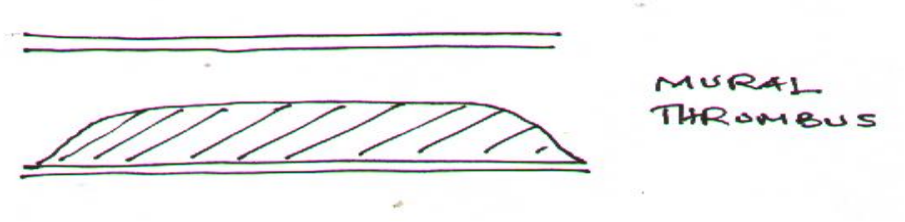


Mural thrombi

- Flowing blood passes over the surface of the mural thrombus and the superficial portion of the thrombus is the seat of infiltration by oxygenated plasma.
- Granulation tissue type capillaries are derived from the vasa and grow very slowly
- The platelets disintegrate and are washed away by the passing stream of blood or phagocytosed.

- There is deposition of fibrin and platelets, which then become vascularized, and eventually there is intimal thickening.

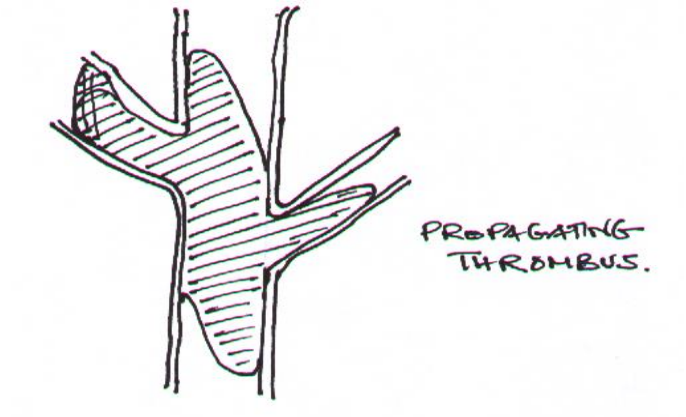
Diagram 4.4: Mural Thrombi



Propagating thrombi

These are thrombi that enlarge and increase in size due to more and more deposition from the constituents of flowing blood and result in occlusion of the vessel and invasion of other vessels.

Diagram 3.5: Propagating thrombi



8.0 SITES OF THROMBUS FORMATION

a) Cardiac thrombosis – occurs in the heart walls and valves
   i. Atria – atrial fibrillation (red thrombus)
   ii. Ventricles – mural thrombosis

Cardiac Thrombus

- Vegetations on the heart valves in infective endocarditis and may lead to emboli occluding peripheral vascular lumens.
- Thrombus underlying myocardial infarction and may cause cerebral vascular accident (CVA) and renal infarction.
- Thrombosis in anodes causing fibrillation.

b) Arterial thrombosis
   i. Atheroma (commonest predisposing factor)
   ii. Aneurysm
   iii. Inflammatory lesions
   iv. Severe hypertension causing necrosis

c) Capillary thrombosis occurs in severe acute inflammation due to endothelial damage and haemoconcentration

d) Venous thrombosis
   i. Deep venous thrombosis (DVT) whose predisposing factors are bed ridden patients, severe injury, post-operative patients, myocardial infarction and post-partum mothers
   ii. Pelvic thrombosis - after child birth, puerperal sepsis and haemorrhoids
   iii. Malnutrition
   iv. Debilitating and wasting diseases and infections e.g. cancers (marantic thrombosis)
   v. Blood disorders – leukaemia and polycythaemia rubra vera
   vi. Inflammation (phlebitis)

9.0 CLINICAL EFFECTS OF THROMBOSIS

The effects of thrombosis depend on site of thrombi, rapidity of formation and the nature of thrombi. The effects result from cardiac thrombi, arterial thrombi, venous thrombi (phlebothrombosis) and capillary thrombi.

Cardiac thrombi

Large cardiac thrombi will cause sudden death through mechanical obstruction of blood flow to vital organs.

Arterial thrombi

Arterial thrombi block arteries causing ischaemia, infarction and gangrene. They may block the coronary artery causing sudden death.

Venous thrombi

Venous thrombi cause effects such as thromboembolism, oedema, poor wound healing, skin ulcers, painful thrombosed veins (thrombophlebitis) and painful white leg[1] (phlegmasia alba dolens).

Capillary thrombi

Small emboli in the microcirculation that can cause disseminated intravascular coagulopathy (D.I.C).

10.0 FATE OF A THROMBUS (NATURAL HISTORY)

1. Lysis or resolution
2. Organization
3. Recanalization
4. Calcification
5. Incorporation
6. Occlusion – causing ischaemia and necrosis
7. Propagation
8. Embolization

[1] Painful white leg occurs due to ileofemoral thrombosis in post delivery cases.

Resolution or Fibrinolysis

The thrombus activates the fibrinolytic system, which releases plasmin that removes the thrombus. Small thrombi are easily dissolved completely but not large one hence the need to accentuate the activity using thrombolytic agents.

Organization

A thrombus in turned into a fibrous tissue depending on whether the thrombus is an occlusive or a mural thrombus. The process of organization involves the activity of the phagocytic cells (neutrophils and macrophages) that liberate proteolytic enzymes. Capillaries grow into the thrombus accompanied by fibroblasts and phagocytic cells that dissolve the thrombus material replacing it with a fibrovascular tissue and the thrombus is excluded from the vascular lumen and becomes part of the vessel wall. It is covered by the endothelium preventing further thrombotic process. The fibrosed thrombus may undergo calcification or hyalinisation.

Calcification

Calcium salts are deposited in the thrombus

Occlusion

The thrombus grows to occlude blood vessels leading to reduced blood flow and circulation causing ischaemia and necrosis.

Recanalization

Clefts appear within the thrombotic material (Clefts lie in the long axis of the occluded segment hence they have the same axis as the blood flow). The clefts become lined by flattened cells of mesenchymal origin, which differentiate into endothelial cells. They link up with one another to form new channels and some degree of blood flow is restored (recanalization).

Propagation

Once s segment of vein is occluded, flow of blood cephaled to the occlusion stops and a stagnant column of blood exist between the point of occlusion and the point cephaled to it where the next venous tributary enters. The stagnant column of blood coagulates forming a “consecutive clot” in continuity with the original thrombosis.

Embolization

The thrombus detaches from the underlying vascular wall and travels in the systemic venous and arterial circulation from one point to another and can impact in vessels whose calibre is less than that of the thrombotic material.

Incorporation

A thrombus may be covered by the endothelium and incorporated in the vessel wall for example when there is a mural thrombus in a large vessel. It explains the formation of atheroma.

Embolism

1.0 INTRODUCTION

Definitions

Embolism *is transference of an abnormal material by the blood stream and its impaction in a vessel causing partial or complete obstruction of the cardiovascular system*.

An **embolus** is an abnormal mass of matter carried in the blood stream and large enough to occlude some vessel. It is transported in the blood stream from one part of the circulation to another. An embolus can also be defined as a detached intravascular solid, liquid or gaseous mass that is carried by the blood to a site distant from its point of origin. Finally impacts in the lumen of vessels with too small calibres to allow the embolus to pass. The commonest emboli are derived from material generated within the vascular system.

2.0 CLASSIFICATION

Emboli can be classified based on a number of factors such as: -

a) The matter in the emboli
   a. Solid – e.g. thrombus, atheromatous material, tumour, tissue fragments, parasites, bacteria and foreign bodies.
   b. Liquid – e.g. fat globules, amniotic fluid and bone marrow.
   c. Gaseous – air and other gases
b) Whether infected or not that is septic or bland/sterile
c) Source
   a. Cardiac e.g. in vegetations of endocarditis
   b. Arterial – in systemic arteries in the brain, kidney, spleen and intestines.
   c. Venous – e.g. pulmonary arteries
   d. Lymphatic
d) Flow of blood
   a. Paradoxical – carried from the venous side to the arterial side through an abnormal communication in the heart and vice versa.
   b. Retrograde – travels against the flow of blood

Our classification will focus mainly on the matter in the emboli but will however take on board the other features such as the source.

3.0 TYPES OF EMBOLISM

1. Thromboembolism
2. Fat embolism
3. Gas/Air embolism
4. Amniotic fluid embolism
5. Atheroembolism
6. Tumour embolism
7. Miscellaneous

3.1. THROMBOEMBOLISM

This occurs when a thrombus (whole or part) detaches from its site and is carried away by the flowing blood to a new site. It may arise from arterial or venous circulation. It accounts for 95 – 98% of emboli. Thromboembolism can be **arterial (systemic) or venous**.

Arterial (systemic) thromboembolism

- Systemic thromboembolism refers to emboli travelling within the arterial circulation.
- Heart (80 –85%) – mural thrombi, vegetations, prosthetic valves and cardiomyopathy
- Arteries – artherosclerosis, aneurysms, pulmonary veins and paradoxical emboli.

a) Arteries - aorta – In sites of atheroma (common in the abdominal aorta).
b) Heart – both the left and right side
    i. Left side effects – kidney, brain and sometimes legs
    ii. Right side - occlusion of pulmonary vessels at the bifurcation of main trunk and pulmonary artery and paradoxical emboli

Effects of arterial thromboembolism

The effects depend on – size of emboli, site of lodgement and adequacy of collateral circulation.

1. Infarctions following necrosis e.g. lower limbs (70 –75%), spleen, kidneys, brain and intestine.
2. Gangrene e.g. in lower limbs
3. Arteritis
4. Aneurysms
5. Myocardial infarction
6. Sudden death

Explain the pathogenesis and clinical presentation of these effects.

Venous thromboembolism

Venous thromboembolism occurs in the venous circulation.

Sites/origin

Veins include Deep veins of legs, Right side of the heart, Upper limbs, Pelvic veins – prostatic, uterine and pelvic plexus, Major sinuses of skull – cavernous sinuses (rare) and Anal region (rare)

Pulmonary Embolism

In pulmonary embolism is where there is lodgement of a thrombus in the pulmonary arterial tree occluding it. Massive pulmonary embolism causes sudden death, moderate embolus will result in pulmonary infarction and small emboli are removed by the fibrinolytic system. The dual blood supply to the lungs through the pulmonary and bronchial arteries with vast anastomosis networks protects the lungs from the effects of moderate and small emboli. The emboli may originate from a number of sources.

Aetiology/origin

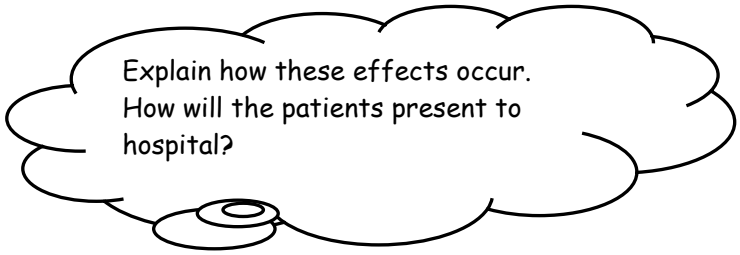
Pulmonary embolism is common in hospitalised or bed-ridden patients. The common sources – large veins of lower limbs (95%) e.g. popliteal, femoral and iliac veins while less common sources – varicosities of superficial veins of legs, pelvic veins (uterine and broad ligament)

Pathogenesis

- A thrombus detaches and is carried to the pulmonary circulation via the right side of the heart
- Large thrombi impact at the bifurcation of the main pulmonary artery
- Small emboli impact in a number of vessels
- Paradoxical embolism

Paradoxical Embolus

A paradoxical embolus is an embolus from the venous side of the circulation that crosses over to the arterial side through heart defects such as ventricular septal defects (VSD) and atrial septal defect (ASD) under the effect of the pressure differences where the pressure of the right is greater that on the left side.



Effects

1. Sudden death
2. Acute Cor pulmonalae
3. Pulmonary infarction
4. Pulmonary haemorrhage
5. Resolution
6. Pulmonary hypertension, chronic Cor pulmonalae and pulmonary arteriosclerosis.

3.2. FAT EMBOLISM

Introduction

Fat globules in circulating blood occlude arterioles and capillaries. Fat embolism commonly affects the kidney, brain and lungs. In majority of cases fat embolism is not fatal. However in about 10% there may be fat embolism syndrome, which usually follows multiple bone fractures. The syndrome which is usually recognized late if fatal develops 3 – 10 days after the trauma with the patient having - acute dyspnoea, petechial haemorrhages (especially over the trunk), mental confusion and reduced platelet count.

Aetiology/causes

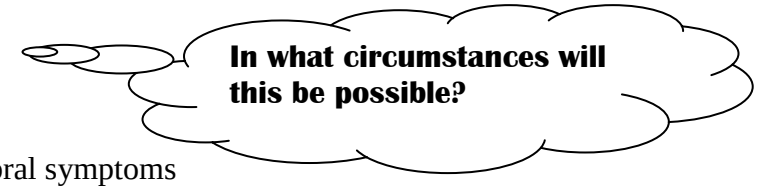
1. Traumatic causes
    a. Trauma to bones – fractures of long bones e.g. humerus, tibia and femur.
    b. Trauma to soft tissue – laceration

2. Non-traumatic causes such as Extensive burns, Diabetes mellitus, Fatty liver, Hyperlipidimia, Pancreatitis, Sickle cell disease, Decompression disease, Inflammation of bones and soft tissues, Extrinsic fat or oils introduced into the body.

Pathogenesis

- In multiple bone fractures, if the veins passing through the compact bone remain open after injury and the subsequent swelling of the surrounding tissues leads to increased local tissue tension which forces emulsified marrow fat particles into the venous channels (mechanical theory). It usually occurs 24-72 hours later.
- Poor natural emulsification of fat results in aggregation of plasma lipids resulting in formation of an embolus (emulsification instability theory) e.g. in prolonged use of steroids, hyperlipidaemia, diabetes and kwashiorkor.
- Injury to blood vessels due to high plasma levels of free fatty acids results in increased vascular permeability that allows entry of fat droplets in the circulation (toxic injury theory). This injury could also be due to necrosis following blockage of capillaries e.g. in sickle cell disease (SCD).

Effects



1. Pulmonary fat embolism
2. Systemic fat embolism e.g. cerebral symptoms

3.3. GAS/AIR EMBOLISM

This occurs when air, nitrogen and others gases produce bubbles in the circulation and obstruct blood vessels causing tissue damage. More than 300 mls of air in circulation is fatal but 400 mls when given slowly the patient may survive and 100 mls given very quickly the patient may die but if given slowly the patient will survive. Gas embolism occurs mainly in two forms namely single embolism e.g. when atmospheric pressure enters the blood and multiple embolism e.g. in Caisson disease.

Air Embolism

Air embolism occurs when air is introduced into venous or arterial circulation.

Venous air embolism

Aetiology/origin

1. Operations and trauma on head and neck e.g. involvement of the jugular veins.
2. Obstetrical operations and trauma – vaginal delivery, caesarean section, abortions and procedures e.g. gas insufflation to test patency of Fallopian tubes.
3. Intravenous infusion of fluids and blood and positive pressure transfusion
4. Infections e.g. Clostridium welchii
5. Angiography

Effects

1. Pulmonary failure
2. Sudden death

The effects depend on amount of air, rapidity of entry, position of the patient and the general condition of the patient.

Arterial air embolism

Aetiology/origin

1. Cardiothoracic surgery and trauma e.g. thoracocentesis, rupture of lungs, penetrating wounds of the lung, artificial pneumothorax.
2. Paradoxical air embolism
3. Arteriography – investigations of artery disease

Effects

Sudden death

1. Marble skin
2. Pallor
3. Altered consciousness

Explain these phenomena.

Decompression Sickness (Caisson's disease)

It is a specialized form of gas embolism. It is known by several names including aeroembolism and diver's palsy.

Aetiology/Causes

1. Divers
2. Workers in caissons[2]
3. Offshore drilling and tunnels
4. Air travel

Pathogenesis

- There is rapid sudden decompression of an individual from either high atmospheric pressure to normal level or from normal pressure to low pressure.
- Divers work under water with high atmospheric pressure and atmospheric gases such as nitrogen, oxygen and carbon dioxide.
- The increased pressure helps in dissolution of the gases into the blood and body tissues.
- When the individual suddenly comes out of the water to the surface (high atmospheric pressure to low pressure) the gases are removed from the body as bubbles especially in fatty tissues with affinity to nitrogen. Oxygen and carbon dioxide easily dissolve out of the blood but nitrogen bubbles may coalesce forming an embolus.

Effects

The effects of decompression depend on depth or altitude reached, duration of exposure, rate of ascent or descent and general condition of the individual. More damage is encountered in situations of sudden decompression from high to normal pressure that from low to normal. Obese people are affected more because nitrogen gas is more soluble in fat that body fluids. The effects can be in an acute or chronic form.

[2] A water tight box for under ground work or water (e.g. construction of bridges)

Acute form

- Acute obstruction of small blood vessels in joints and skeletal muscles
- Patient bends up in bed due to pain
- Patient chokes due to accumulation of bubbles in the lungs
- Vertigo and coma as cerebral effects
- Sometimes coma

Chronic form

The chronic form of decompression occurs due to foci of ischaemic necrosis throughout the body. The features of the chronic form are: -

- Avascular necrosis of bones – head of femur, tibia and humerus
- Neurological – paraplegia and paraesthesis
- Lung involvement – haemorrhage, oedema, emphysema and atelectasis
- Skin manifestations – itching, patchy erythema, cyanosis and oedema.

3.4. AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism occurs during labour due to entry of amniotic fluid into the maternal circulation with subsequent involvement of the lungs. Uterine contractions during labour create high pressure in the uterus able to force amniotic fluid into the blood stream via open maternal placental sinuses.

Pathogenesis

- The foetal head engagement in the pelvis acts as a cork.
- With each descend the pressure inside the pelvic cavity increases
- Uterine contractions force amniotic fluid into the blood stream at a high pressure through the maternal sinuses and a vent in the amniotic membrane.
- The amniotic fluid and its contents (epithelial squames, vernix caseosa, lanugo hair, bile from meconium and mucous) enter the circulation to reach the right side of the heart.

Effects

1. Respiratory distress due to plugging of pulmonary capillaries with keratin and lanugo from the amniotic fluid causing maternal respiratory distress. Can also be due to haemorrhage and oedema.
2. Bleeding tendencies as sudden release of amniotic fluid with has increased thromboplastin into the maternal circulation causes multiple intravascular thrombosis.
3. Thrombosis causes reduced fibrinogen levels leading to post-partum Haemorrhage (PPH)

Clinical features (syndrome)

- Sudden respiratory distress and dyspnoea
- Deep cyanosis
- Cardiovascular shock
- Convulsions, Coma
- Unexpected death

3.5. ATHEROEMBOLISM

This occurs as a result of atheroma plaques that get erodes and the fragments detach from their site of formation. These plaques contain cholesterol crystals, hyaline debris and calcified material.

Aetiology/origin

- Hyperlipidaemia

Pathogenesis

- High levels of lipids in blood lead to deposition of the lipids on the internal surface of the vessel forming artheromatous plaques.

Effects

1. Ischaemia, atrophy and necrosis of tissues
2. Infarcts in organs
3. Gangrene
4. Hypertension

3.6. TUMOUR EMBOLISM

Malignant tumours cells invade tissues through the local blood vasculature. Fragments of the tumour cells mat break off and are carried by the flowing blood to local and distant sites in the body. This accounts for the metastasis of tumours e.g. carcinoma of the lungs and malignant melanoma.

3.7. MISCELLANEOUS EMBOLI

Tissue Emboli

This occurs when a piece of tissue breaks off from a tumour mass, placental tissue or an atheromatous plaque.

Septic/Bacterial Emboli

Occur as a result of infective agents e.g. bacterial vegetations in infective endocarditis

Parasitic Emboli

- Clumps of parasites in cerebral malaria
- Microfilariae in pulmonary capillaries

Foreign Body

- Glass beads and chalk in drug addicts

4.0 EFFECTS OF THROMBOSIS & EMBOLISM

The primary effect is reduction of blood flow to the affected tissues/region causing ischaemia and infarction. Overall effects of the magnitude of ischaemia will depend on: - size of occluded

vessel, presence or absence of collateral circulation, presence of double circulation e.g. the lungs and the liver, speed of onset, size of embolus and type of tissue or organ affected e.g. a 5 mm infarct in the brain will have a greater effect than a 5 mm infarct in the harm strings.

The Heart

- Cardiac failure due to infarction – a big infarct will cause cardiac arrest and myocardial rupture while a small infarct leads to ventricular fibrillation

The Brain

- Infarction leads to a state of unconsciousness

The Kidney

- Renal failure occurs

Intestines

- Bleeding per rectum.

Lungs

- The effect depends on the size of the emboli
    - Massive emboli causes breathlessness, hypotension Patient collapses/instant death
    - Small emboli ("showers") will lodge in the lung and trigger the process of inflammation process. This results in fibrosis that causes pulmonary hypertension and subsequent Cor-pulmonalae (right sided heart failure secondary to chronic lung disease).

Lesson 4: Ischaemia and Infarction

Learning Outcomes

At the end of the lesson the learner should be competent to: -

1. Describe the causes of ischaemia
2. Describe the changes seen in ischaemic tissues
3. Describe the effects of ischaemia
4. Describe factors influencing ischaemia
5. Describe the causes and pathogenesis of infarction
6. Explain the pathology of infarction
7. Describe the outcome of infarct
8. Describe the organ changes in infarction

Ischaemia

1.0 INTRODUCTION

Ischaemia can be defined as deficient blood supply to part of a tissue or a state of lowered perfusion relative to the metabolic demands of a tissue. Complete ischaemia occurs when there is complete cessation of blood flow while partial ischaemia is when there is abnormally low blood supply to a tissue.

Ischaemia is usually localized in an organ, patch of a tissue or part of the body. It is most often caused by some local interference with the perfusion of the organ or tissue concerned. Occasionally it is generalized when it is associated with a fall in cardiac output.

2.0 CAUSES

1. Generalized ischaemia – results from situations affecting the heart
2. Localized ischaemia due to arterial obstruction, venous obstruction or obstruction in the microcirculation

2.1.General Ischaemia

Inadequate cardiac output deprives the brain of blood supply causing hypoxic injury to the brain cells. 15 seconds of reduced blood supply to the brain causes impaired consciousness, 4 minutes results in irreversible ischaemic damage of brain cells and in 8 minutes brain death is inevitable. The reduction in cardiac output can be as a result of heart block, ventricular failure and fibrillation.

This occurs in circumstances where anoxia is generalized i.e. all organs of the body suffer simultaneously. It is usually associated with respiratory disease, cardiovascular disease and others causes of anoxia such as anaemia.

There are two forms of generalized ischaemia, which are considered as temporary general ischaemia.

1. Transient stoppage of the heart under surgical anaesthesia.

In this instance resuscitation is possible (cardiac massage and cardiac stimulants) and the heart beat resumes after a few minutes. If resuscitation is suspended for a longer period of time/period it is dangerous, as resuscitation proves very difficult because the brain is the most sensitive to circulatory disturbance as neurons serving subserve consciousness fail immediately. Neurons of the vital respiratory and vasomotor centre resist anoxia for 30 minutes.

2. Develop after badly administered nitrous oxide anaesthesia

2.2. Localized Ischaemia

Causes in the Arteries

This results from obstruction in arterial blood supply.

Causes

1. Luminal occlusion – Thrombosis, Embolism

2. Causes in arterial wall
   a) Vasospasm e.g. Raynaud's disease
   b) Hypothermia
   c) Arteriosclerosis
   d) Polyarteritis nodosa (PN)
   e) Thromboangitis obliterans (Buerger's disease)
   f) Severed vessel wall

3. Outside pressure on an artery – ligature, tourniquet, tight plaster of paris (p.o.p), bandages torsion

Causes in the veins

1. Luminal obstruction mainly by thrombosis and embolism as in: -
   a) Extensive mesenteric venous thrombosis causing infarction of the small intestines
   b) Cavernous sinus thrombosis leads to retinal vein thrombosis causing blindness
   c) Thrombosis of the superior longitudinal sinus as seen in severely dehydrated children
2. Causes in the vessel wall - varicose veins on the legs
3. Outside pressure on the vein
   a) Strangulated hernia
   b) Intussusception
   c) Volvulus

Causes in the microcirculation

1. Luminal causes
   a) Red cells in Sickle cell anaemia, red cells parasitized by malaria and autoimmune haemolytic anaemia.
   b) White blood cells in leukaemia
   c) Fibrin deposition where disseminated intravascular coagulopathy (DIC) has occurred.

d) Fat embolism
e) Gas emboli in decompression sickness
f) Antigen-antibody complexes

2. Causes in the microvasculature wall
   a) Vasculitis e.g. in Arthus reaction, polyarteritis nodosa and septicaemia
   b) Physical damage e.g. frost bite

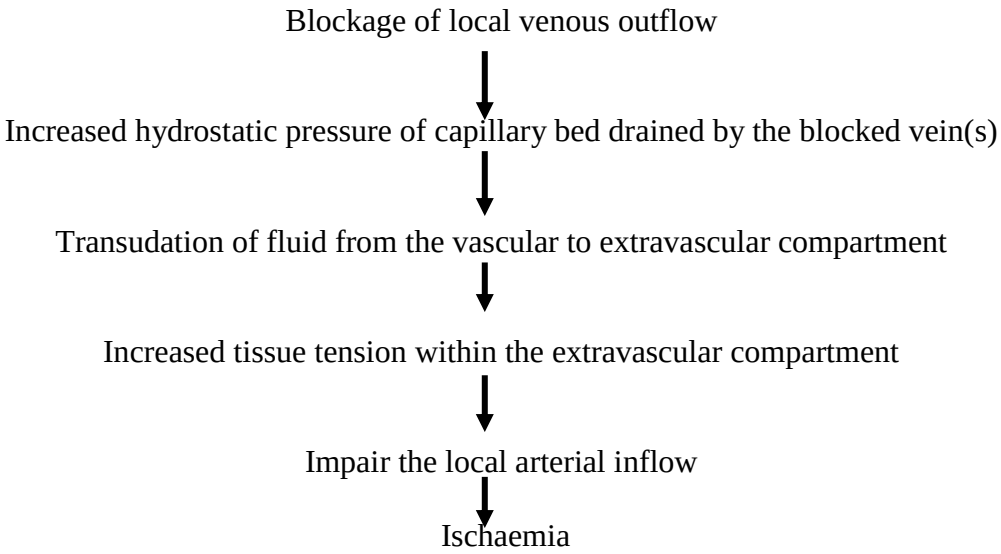
3. Outside pressure e.g. decubitus ulcers (bedsores).

3.0 PATHOGENESIS

Venous

Obstruction of the venous drainage leads to engorgement and obstruction to arterial blood supply and eventual ischaemia.

Diagram 4.1: The pathogenesis of ischaemia due to venous obstruction



The tissues affected are intensely congested and possibly even haemorrhagic.

Microcirculation

There is occlusion of arterioles, capillaries and venules resulting in ischaemia. The mechanism involves both arterial and venous obstruction.

Arterial

Obstruction of arterial inflow results in a wide spectrum of functional and structural disturbances ranging from no detectable effects to extensive tissue necrosis. However, there are no functional or structural effects when the collateral arterial supply to the target organ is excellent.

Functional disturbances occur when the collateral supply is good enough to maintain adequate blood supply at basal metabolic demands of the tissue but increased demand leads to a pronounced state of ischaemia e.g. angina pectoris on the heart and cramp-like pain in the calf

(intermittent claudication). Significant changes in functional occur in ischaemia when there is loss of cells and abnormal or deficient function of the surviving cells.

Severe ischaemia causes structural damage to cells and tissues ranging from patchy loss of parenchyma cells to massive necrosis

4.0 FACTORS DETERMINING MAGNITUDE OF ISCHAEMIA

The degree of ischaemia is determined by interacting variables such as: -

1) Anatomy of local blood supply structures
2) General and cardiovascular status
3) Type of tissue affected
4) Speed of development of ischaemia
5) Degree of vascular occlusion
6) Metabolic demand of the under-perfused tissue
7) State of potency of the collateral blood supply

Anatomy of local blood supply

Some organs/tissues have no collateral blood supply and are perfused by end arteries e.g. the retina (central retinal artery and the brain (arteries within the cerebral cortex). Other tissues such as the liver and lungs have double arterial blood supply. The collateral blood supply becomes less significant in the event of severe infection or damage of the vessels.

There are four different patterns of arterial blood supply namely: -

a) Single arterial supply without anastomosis (functional end-arteries) e.g. central artery of the retina and interlobular arteries of the kidney.

b) Single arterial supply with rich anastomosis where there is the capacity of channels re-opening to allow blood flow in the event of an obstruction e.g. superior mesenteric artery (supplies small intestines) and inferior mesenteric artery (supplies distal colon).

c) Parallel arterial supply e.g. blood supply to the brain (Circle of Willis) and supply to forearm (radial and ulnar arteries).

d) Double (dual) blood supplies e.g. lungs (bronchial circulation and pulmonary arteries) and liver (portal circulation and hepatic arterial flow).

General and cardiovascular status

The general wellbeing of an individual and the competence of the cardiovascular system dictate the effects of ischaemia. Conditions such as anaemia, hypoxaemia, blood loss, shock, cardiac failure and senility do fuel the magnitude of effects.

Type of Tissue affected

Tissues vary in capacity to withstand reduced arterial perfusion as they posses' different needs as per their metabolic demands. The brain is the most sensitive with deprivation of oxygen for more

than 3 – 4 minutes causing irreversible damage to nerve cells. The myocardium is very susceptible. Both the heart and brain have poor collateral blood supplies and their cells are not able to regenerate. Mesenchymal tissues are quite resistant to effects of ischaemia as compared to parenchymal cells of organs. Tissues highly vulnerable to effects of ischaemia are the brain (cortical neurones), heart (myocardial cells) and kidney (proximal convoluted tubules).

Speed of onset of underperfusion

Rapid speed has some severe effects as little time or no time is available for collateral vessels to open up to supply blood.

Degree of Vascular occlusion

Complete occlusion of arterial lumen causes more extensive damage than does severe stenosis. The more proximally the occlusion is in a given arterial tree the greater the area of tissue affected.

5.0 EFFECTS OF ISCHAEMIA

The effects of ischaemia can be gradual ischaemia causes – fibrous tissue formation (replacement fibrosis) or sudden ischaemia causes necrosis and infarction. The effects are variable and range from no change to sudden change. The effects seen are no change, functional disturbances, cellular changes and sudden death.

No change

The collateral channels open up to allow adequate supply of blood to tissues.

Which organs in the body are well served with collateral circulation?
Give examples of circumstances that lead to failure of collateral blood supply to these organs failing hence the organs becoming ischaemic

Functional changes

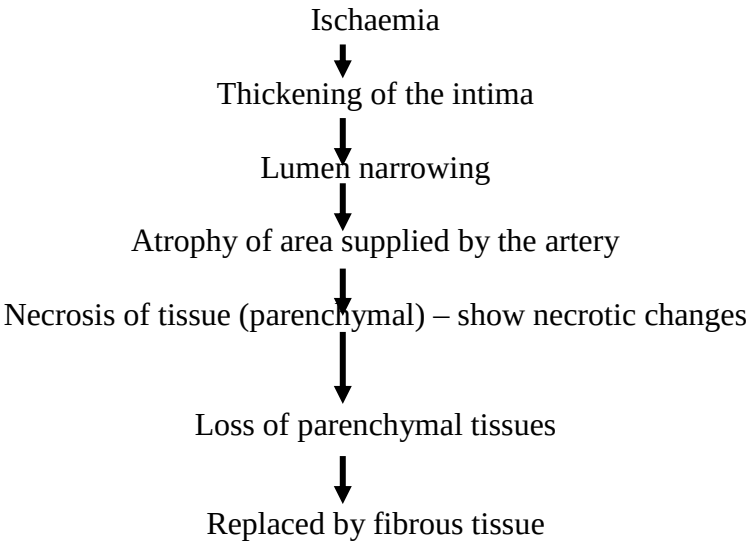
The collateral circulation is capable of sustaining blood supply under normal activity but fails to sustain the supply due to effects of exertion for example Angina pectoris.

Think of examples at the various wards at the Kisii Level 5 Hospital

Cellular changes (Structural)

Partial ischaemia causes cellular changes e.g. cloudy swelling, fatty change, and atrophy and replacement fibrosis while complete ischaemia results in necrosis and infarction. *Replacement fibrosis is seen in the kidney (ischaemic atrophy), myocardium (ischaemic fibrosis), liver (cirrhosis) and brain (leads to softening followed by proliferation of glial tissue – replacement fibrosis)*

Diagram 4.2: Diagrammatic Representation of replacement Fibrosis



Sudden death

Sudden death occurs when ischaemia of vital organs is encountered e.g. myocardial infarction and cerebral infarction.

Infarction

1.0 INTRODUCTION

Infarction is tissue necrosis resulting from reduced blood supply. The word in *farcire* means to stuff in Latin. An infarct is an area of ischaemic necrosis. *An infarct is an area of ischaemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue.*

2.0 CAUSES

Infarction occurs as a result of the narrowing or occlusion of blood vessel lumen due to emboli, thrombosis and atherosclerosis. The size of an infarct depends on: - amount of ischaemic tissue, severity and duration of ischaemia and susceptibility of cells involved.

3.0 PATHOGENESIS

1) Localized hyperaemia
   - ➲ Occurs due to local anoxaemia due to obstruction

2) Swelling – oedema and haemorrhage.
   - ➲ Due to obstruction the blood pressure distal to the infarct reduces to zero leading to influx of blood from capillaries, venous side and anastomosis to fill the empty arterial side. There occurs intense congestion of the infarct.
   - ➲ The amount of haemorrhage is marked in the lungs and spleen and less extensive in the heart and kidneys.

3) Progressive autolysis and haemolysis of the red cells
4) Cellular changes – coagulative necrosis occurs in 12-48 hours.
5) An acute inflammatory reaction and hyperaemia
6) Blood pigments – haematoidin and haemosiderin
7) Ingrowth of granulation tissue
   - ➲ The granulation tissue grows from the margins of the wound forming a scar.
   - ➲ Dystrophic calcification can occur and in some cases e.g. in the brain liquefaction takes place.

4.0 TYPES OF INFARCTS

There are two types of infarcts: - red (haemorrhagic) and pale (white) based on the colour of the infarct. The colour depends on amount of blood supply to the tissue, collateral circulation and compactness of tissue or organ involved. Pale infarcts results form arterial occlusion as seen in compact organs such as the kidneys, heart and spleen while red ones occur in loose tissues such as the lungs following arterial obstruction of intestines as a result of arterial or venous occlusion.

Pathological Changes

Pathological changes are based on site, shape, microscopy and macroscopy

Site

Kidney, spleen, heart, lungs, brain, retina, intestines and liver

Shape

- Wedge shaped corresponding to the area of distribution of occluded artery
- The base of the wedge is towards the surface of the organ
- The apex is at the point of occlusion

Macroscopy

The cut surface is dry, granular and friable.

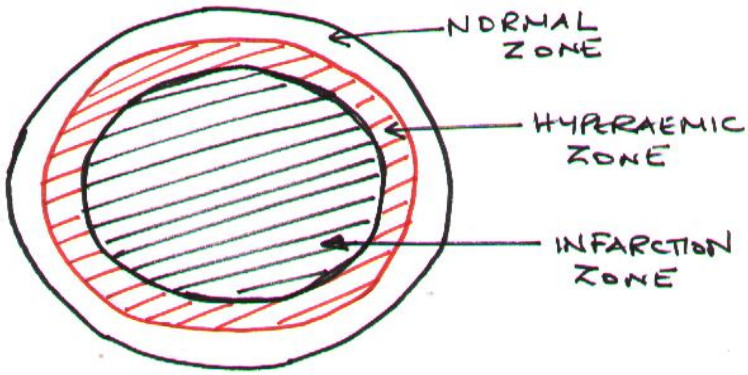
Microscopy

At the area of infarction three zones are visible - the infarction, hyperaemic and normal tissue zone. The infarction zone exhibits: - coagulative necrosis, degenerating changes, ill-defined cell boundaries and pale cytoplasm.

Hyperaemic zone shows inflammatory changes: -
- Dilated blood vessels
- Fibrin exudate
- Leucocytes – polymorphs and lymphocytes
- Macrophages

The normal zone is the zone beyond the hyperaemia

Diagram 4.3: An Infarct



5.0 MORBID CHANGES IN ORGANS

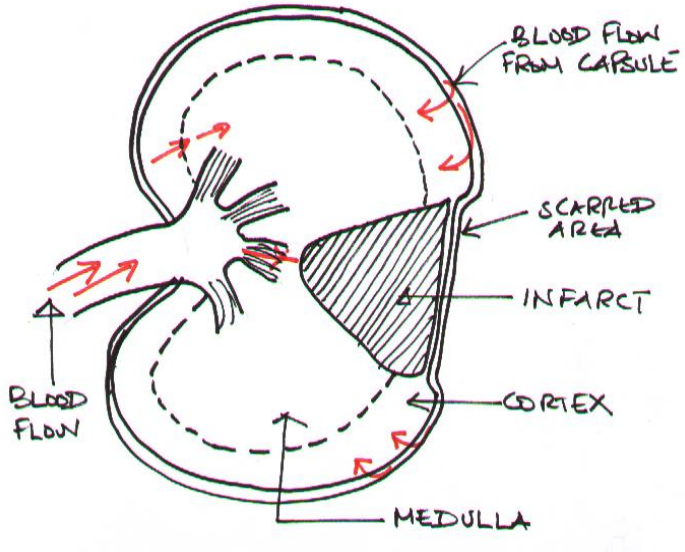
RENAL INFARCT (KIDNEY)

Renal infarct is common in bacterial endocarditis, myocardial infarction and aortic aneurysm nut less common in arteritis, renal artery atherosclerosis and sickle cell anaemia. The main causes are embolism, thrombosis and artherosclerosis.

Gross Appearance

- Pale depressed areas irregularly demarcate the cortex.
- The kidney surface is not involved as blood is supplied from vessels entering from the capsule.
- The cut surface shows central pale area
- The infarct is wedge shaped with the base in the cortex and the apex in the medulla.
- A rim of uninvolved cortex separates the infarct from the capsule.

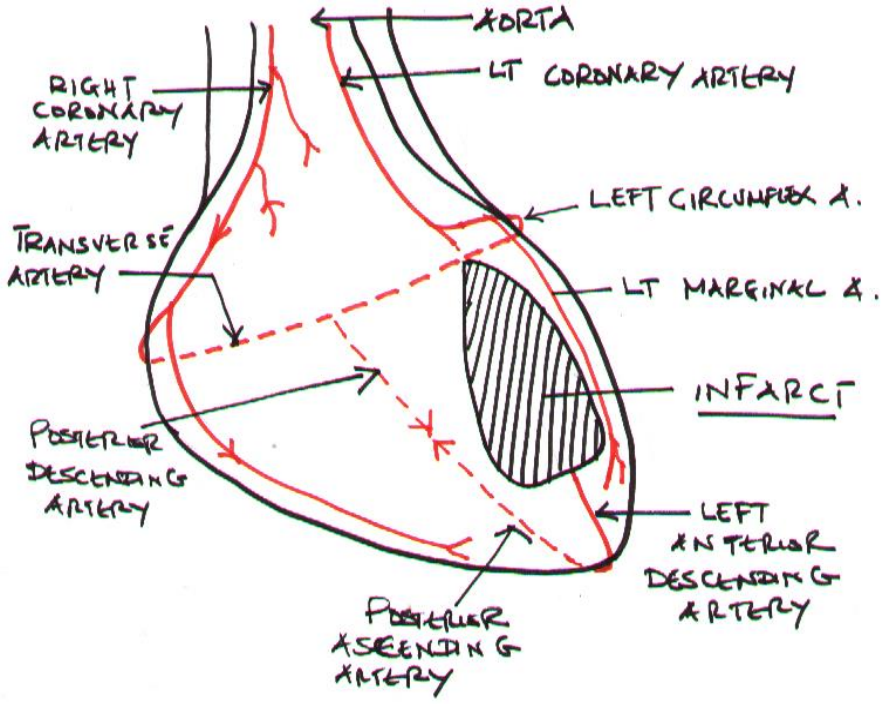
Diagram 4.4: Renal Infarct



MYOCARDIAL INFARCT (HEART)

Myocardial infarction results from coronary artery occlusion due to thrombosis, embolism, atherosclerosis and syphilitic aortitis.

Diagram 4.5: Myocardial Infarction



Gross appearance

- The dead tissue undergoes coagulative necrosis gradually becoming pale
- There scattered haemorrhagic areas
- Polymorphs infiltrate the margins (signifying inflammation)
- Granulation tissue formation

Causes of death as a result of myocardial infarct are ventricular fibrillation, cardiac failure and cardiac arrthymias.

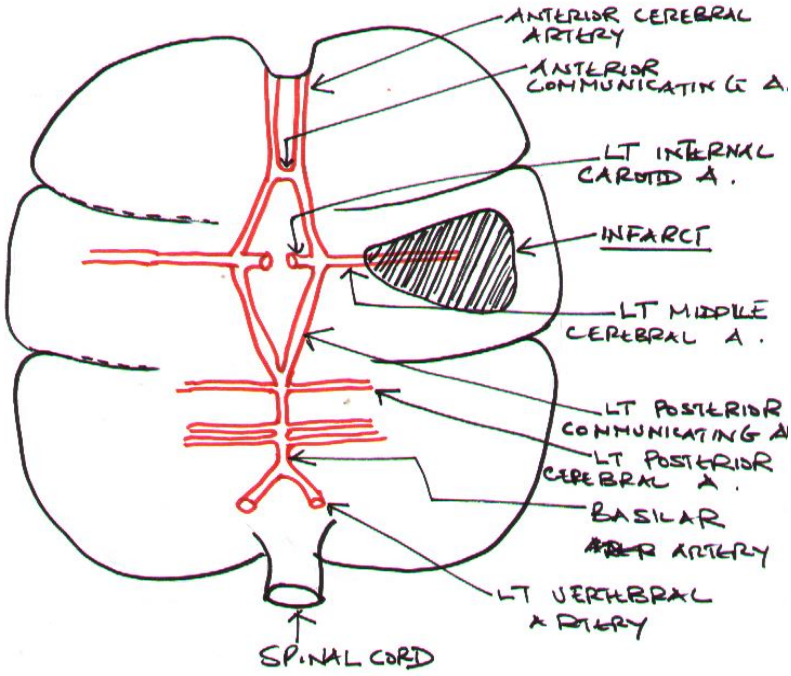
CEREBRAL INFARCT (BRAIN)

The cerebral arteries are considered end arteries and the brain tissue is highly susceptible to ischaemia. It commonly involves the middle cerebral arteries and the internal capsule. Cerebral infarcts result from embolism, thrombosis and atherosclerosis

Gross appearance

- The infarct may be pale or haemorrhagic
- Dead tissue undergoes autolytic digestion (softening/liquefaction)
- Necrotic tissue is gradually removed by macrophages and not by organization

Diagram 4.6: Cerebral Infarct



SPLEENIC INFARCT (SPLEEN)

Spleenic infarct is a very common infarct.

Causes

- Occlusion of major spleenic artery due to thrombosis, embolism and atheroma
- May occur in atheroma, bacterial endocarditis, spleenic anaemia, leukaemia and tropical spleenomegally syndrome (TSS)

Gross appearance

- Large single or multiple infarcts
- Dark red due to congestion but later they become pale
- Organization and fibrosis occurs

PULMONARY INFARCT (LUNGS)

Causes

- Passive venous congestion due to local thrombosis and chronic cardiac disease.
- Post-operative embolism (commonest cause) – thrombosis and embolism
- Infective embolism from systemic veins or the right heart chambers

The lungs usually have protection against infarction through: -

1. Gas exchange in peripheral ramifications of the respiratory passages supply oxygen
2. The dual blood supply with numerous anastomoses between bronchial artery and pulmonary artery.

Gross appearance

- The infarct is airless, solid, raised, firm and red.
- Is removed by organization

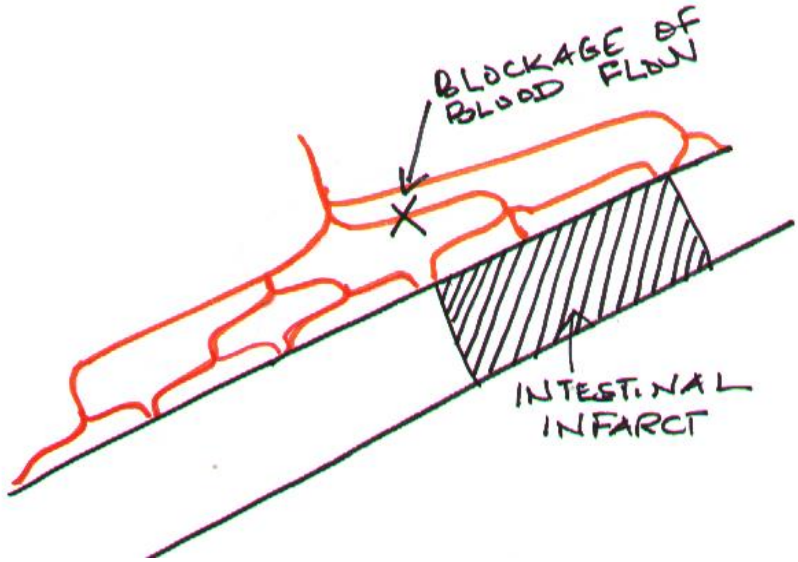
INTESTINAL INFARCT

Intestinal infarcts occur as a result of occlusion of superior mesenteric artery due to emboli (from the heart), thrombosis and mechanical obstruction (twisting strangulated hernia, volvulus and intussusceptions.).

Gross appearance

- The necrotic wall is congested, oedematous and haemorrhagic
- Microorganisms invade the dead tissue causing severe toxaemia

Diagram 4.7: Intestinal Infarct



Think of infarcts in the liver, retina and the limbs.

6.0 OUTCOME OF INFARCT

1. Absorption – by autolysis and phagocytosis
2. Organization and fibrosis (scarring)
3. Softening
4. Dystrophic calcification
5. Septic emboli causing pyaemia and abscess
6. Gangrene
7. Organ Failure

With specific clinical examples, discus the effects of the outcomes of infarction on various organs and systems.

Lesson 5 Haemorrhage (Bleeding) & Haemostasis (Blood Clotting)

Learning outcomes

The learner should be able to: -

1. Describe causes and effects of haemorrhage
2. Explain how the body responds to haemorrhage
3. Describe the process of haemostasis
4. Describe the process of blood clotting.
5. Evaluate factors leading to poor clotting and bleeding disorders

Haemorrhage

1.0 INTRODUCTION

Haemorrhage is escape of blood from a vessel. The bleeding may occur externally or internally into serous cavities. The blood can escape to the free surface and into tissues and cavities following a breach in the vessel wall. The red cells escape by diapedesis to form small haemorrhagic areas (Haemorrhage by rhexis).

Haemorrhage is an emergency in medicine, surgery and obstetrics and gynaecology. The danger of bleeding is as a result of the severity of haemorrhage, suddenness of blood loss and the site of haemorrhage. Healthy adults can loss 550 mls of blood with no significant disability while, 25% loss causes significant hypovolaemia and 50% loss occurring suddenly reduces the circulation significantly and death occurs if therapeutic fluid replacement is not undertaken immediately. Haemorrhage distributed over many hours or days allows adaptive compensatory mechanisms to take place lessening the functional disturbances that would arise.

2.0 NOMENCLATURE IN HAEMORRHAGE

The naming of haemorrhages is done according to: - size, extent, site

Table 3.1: Names and description of haemorrhage sites

Name	**Description**
a. Spontaneous massive Haemorrhage	Rupture of large vessel or aneurysm with a dilated vessel or thin wall
b. Petechiae	Less than 2 mm in diameter. Seen on the skin and serous membranes.
c. Purpura	2 – 5 mm in diameter. Seen on the skin and mucous membranes.
d. Ecchymosis	Cutaneous Haemorrhage of more than 5 mm in diameter.
e. Epistaxis	Bleeding from the nose
f. Haematemesis	Vomiting blood – fresh or altered
g. Malena	Black coloured or tarry stools due to blood digestion after Haemorrhage into the bowel. The colour is due to formation of black sulphide iron.

h. Haemoptysis	Spitting of blood from lungs or bronchial tree
i. Haematuria	Passing blood in urine
j. Haemoglobinuria	Haemoglobin in urine
k. Menorrhagia	Excessive menstrual flow
l. Metrorrhagia	Irregular uterine bleeding
m. Polymenorrhagia	
n. Cerebral Haemorrhage	Bleeding in brain
o. Intracranial Haemorrhage	Bleeding into the cranium
p. Haematomyelia	Bleeding into spinal cord
q. Haematorrhacins	Bleeding into meninges
r. Ante-partum Haemorrhage (APH)	
s. Post-partum Haemorrhage (PPH)	
t. Haemothorax	
u. Haematosalpinx	
v. Haematocoele	Bleeding into the tunica vaginalis
w. Subdural Haemorrhage	
x. Subrachnoid Haemorrhage	
y. Extradural Haemorrhage	
z. Haematoma	Extravasation of blood into tissues with resultant swelling.

Task 1: Find the definitions or descriptions of the names of the bleeding sites in table 1.

3.0 CAUSES

1. Trauma
   a. Mechanical – cuts, tears, bruises in tissues
   b. Surgical operations
      i. Primary haemorrhage – occur during operation
      ii. Reactionary haemorrhage – occur within first 24 hours
      iii. Secondary haemorrhage - occur after one week

2. Obstetric/gynaecologic
   a. Delivery and abortions
   b. Menstruation and menstrual disorders
   c. Antepartum and postpartum haemorrhage (APH and PPH)

3. Erosion
   a. Rupture of vessels
   b. Tumours

4. Disease of the vessel wall
   a. Arteriosclerosis
   b. Aneurysms
   c. Inflammatory lesions – typhoid fever, peptic ulcer.

5. Elevated pressure within the vessels
   a. Cerebral and retinal haemorrhages in systemic hypertension
   b. Varicose veins – oesophageal varices, haemorrhoids

6. Haemorrhagic diatheses (Bleeding Disorders)

a. Deficiency of platelets (purpura) – reduced platelets (purpura is a condition of petechial haemorrhage into the skin and mucous membranes). Deficiency of platelets is called thrombocytopenia. This could be primary or secondary in origin.
   i. Decreased production of platelets as in diseases of the bone marrow such asaplastic anaemia, disseminated cancer e.g. leukaemia, ineffective production – megaloblastic states and bone marrow failure – drugs, X-rays
   ii. Destroyed platelets (Decreased platelet survival) as seen in autoimmune idiopathic, immune induced destruction by Secondary immune reactions – S.L.E, leukaemia Viral infections, drugs (e.g. quinine), infections (e.g. HIV), D.I.C
   iii. Sequestration - Platelets trapped in the spleen in hyperspleenism.
   iv. Dilutional – massive transfusion of stored blood cause relative reduction in the number of platelets
   v. HIV

b. Defective clotting mechanism
   i. Haemophilia (Factor VIII deficiency) and Christmas disease
   ii. Hypoprothrombinaemia
   iii. Reduced fibrinogen (fibrinogenaemia)

c. Damage to capillary endothelium (fragility of blood vessels)
   i. Inflammation – bacteria and toxins e.g. streptococcal septicaemia, typhoid fever, osteomyelitis, meningococcal meningitis and infective endocarditis.
   ii. Injury – mechanical, venoms, chemicals (benzol, arsenic)
   iii. Vitamin C deficiency
   iv. Anaphylaxis

7. Liver disease
8. Vitamin K deficiency
9. D.I.C

4.0 EFFECTS OF HAEMORRHAGE

The effects of haemorrhage occur in three stages /categories
1. The immediate effects
2. Delayed effects
3. Recuperative stage

4.1. Immediate Effects

Immediate effects of haemorrhage occur within one hour of bleeding and comprise of two reactions namely the **faint** and **vasomotor compensations**.

The Faint

Fainting results from a circulatory crisis or failure due to volume loss and is influenced by psychological factors such as pain, fear, fatigue and sight of blood. It is a normal reaction to severe sudden haemorrhage. The faint reaction is precipitated by reflex mechanisms via the autonomic nervous system

Mechanism of Fainting

1) After blood loss, sympathetic stimulation causes sudden lowering of peripheral arteriolar resistance (especially in the skeletal muscles) and dilatation of coronary vessels and skeletal muscle vessels. Normally there is little or no reduction in cardiac output when little blood is lost because constriction of veins and venous reserves release stored blood (during the compensatory stage).

2) Because of the increased vascular bed blood is then diverted to the dilated vascular bed. This diversion of blood into the dilated vascular bed causes a vaso-vagal attack that leads to a sharp fall in arterial blood pressure causing temporary failure of cerebral function resulting in a state of unconsciousness (**the faint**).

Vasomotor Compensation

Loss of 400 – 550 mls of blood leads to a 10% decrease in systolic blood pressure while a large loss of blood leads to a significant fall in blood pressure. Vasomotor compensatory mechanisms are mainly the **autonomic nervous** system and **hormonal** systems

Autonomic Nervous System

1) A fall in arterial pressure leads to a reduction in the frequency of nervous impulses from the carotid and aortic sinuses receptors reducing the inhibitory effect exerted by the cardiac centre upon the heart muscles hence an increased heart rate (pulse rate).

2) The central inhibition of the vasomotor centre becomes reduced leading to marked peripheral vasoconstriction hence increasing the peripheral resistance.

3) There is post-haemorrhagic vasoconstriction occurs in the skin, salivary glands, alimentary tract and the kidney conserving water hence improving the blood volume and blood pressure.

4) Blood is diverted to the heart and brain.

Hormonal

The hormonal mechanisms supplement the reflex mechanisms. The hormones involved are: - **adrenaline** (from the adrenal glands), **renin** (from the kidneys), **adreno-cortico-trophic-hormone, ACTH**, (from the anterior pituitary gland) and **2-3 Diphosphoglycerate**

Adrenaline

1) Its release results from nervous impulses from the splanchic nerves
2) Elevates the blood pressure by increasing the cardiac output and peripheral resistance by causing vasoconstriction
3) Increases efficiency of muscular contractions
4) Increases ACTH release

Renin

Rennin causes vasoconstriction, water and salt retention improving the blood volume and subsequently the blood pressure.

ACTH

Increases glucosteroids, which maintain capillary integrity and reduce effects of mediators of inflammation.

2-3 Diphosphoglycerate

Increases oxygen release from the red blood cells

4.2. Delayed Effects

These are the compensatory adaptations, which occur in 24-48 hours and result in haemodilution due to reabsorption of fluid from interstitial spaces. They are directed at maintaining the blood volume to sustain the circulatory volume and blood pressure. This is when pallor becomes evident on physical examination.

4.3. Recuperative Stage

The recuperative stage is geared to restoring the blood volume and composition. It lasts for many weeks depending on the extent of blood loss and the patient's ability to replace blood cells and plasma proteins. The following occur during recuperation: -

1. Changes in erythrocytes and leucocytes
    a. Bone marrow - Increased activity with more leucopoetic than erythropeoitic tissue because of the differences in the life span of the various cells.
    b. White blood cells (WBCs) – leucocytosis
    c. Appearance of normoblasts and reticulocytes in circulation (in severe haemorrhage)
    d. Red blood cells (RBCs) – microcytic, hypochromic
    e. Replacement of RBCs is a gradual process fro many weeks that depends on severity of anaemia at the height of haemodilution and the nutritional reserve for haemoglobin and plasma proteins.
2. Plasma proteins replacement
    a. Re-opening of partially closed capillaries with trapped plasma proteins
    b. Rapid liberation from the liver storage
    c. Synthesis by cells
3. Nutrition
    a. Provide a balanced diet during the recuperation. Why?

Haemostasis

1.0 INTRODUCTION

Haemostasis is cessation of bleeding (*Haemo* = blood; *stasis* = standing). Blood should remain fluid within the cardiovascular system but be capable of local haemostasis where there is formation of an adhesion plug, which prevents bleeding after injury. Breakage of the vascular endothelial lining of a vessel exposes collagen proteins from the subendothelial connective tissue initiating three separate but overlapping haemostatic mechanisms namely **vasoconstriction**, **platelet plug formation** and **formation of fibrin protein around the platelet plug**.

Normal haemostasis results from a set of well-regulated processes that maintain blood in a fluid (clot Free State in normal blood vessels) and induce a rapid and localized haemostatic plug at the site of vascular injury. The pathologic opposite to haemostasis is **thrombosis** which involves inappropriate activation of normal haemostatic process e.g. formation of a thrombus in non-injured tissues.

2.0 VESSEL REPAIR

Minor Repair

This occurs as a result of the wear and tear from normal activities. The injury or loss of endothelial cells exposes collagen proteins from the subendothelial connective tissue, which triggers the process of clot formation. The repair is rapid and instantaneous through the process of platelet adhesion and growth of endothelia over the platelet layer. In situations of thrombocytopenia (reduced platelets) this is not achieved and spontaneous Haemorrhage (bleeding) occurs in the micro-vessels. In haemophilia, coagulation and clotting is defective due to poor solid fibrin formation.

Major Repair

Occurs when there is complete severance of blood vessels and the bleeding is temporarily stopped by vasoconstriction. Later the platelets' sticking to the collagen and the gradual deposition of fibrin forms a haemostatic plug, which later is covered by the extending vascular endothelium. Thereafter the process of organization removes the plug gradually.

3.0 HAEMOSTASIS

The most important players in the process of haemostasis are the **platelets**, **vascular endothelium**, **clotting**/**coagulation** process (fibrin deposition) and **plasmin/fibrinolytic** system

3.1. The Vascular Endothelium

Introduction

The endothelial cells play a significant in several spects of normal haemostasis as they have both anticoagulant and procoagulation activities. Normal flow of liquid blood is maintained by endothelial antiplatelet, anticoagulant and fibrinolytic properties.

Following injury or activation the endothelial cells have several procoagulation activities such as endothelial actvitation by infectious agents, haemodynamic factors and plasma mediators (cytokines). Damage to the endothelial lining exposes activated factors to blood coagulation factors.

Anti-thrombotic Properties

In the absence of injury endothelial cells maintain a conducive environment for liquid blood flow through mechanisms that prevent platelet adhesion and aggregation, interfere with coagulation cascade and actively break blood clots.

Anti-platelet Effects

An intact endothelium prevents platelets and coagulation factors (plasma) from getting in contact with the highly thrombogenic subendothelial tissue. Endothelial cells have *adenosine disphosphatase* which degrades ADP thus inhibiting platelet aggregation.

Anticoagulant Effect

This is mediated by heparin-like substance which interacts with antithrombin III to inactivate thrombin, factor Xa and other coagulation factors.

Fibrinolytic Effects

Endothelial cells synthesize tissue-type plasminogen activator (tPA) promoting fibrinolytic activities that clear fibrin deposits from endothelial cells.

Prothrombotic Properties

Platelet Effects

Endothelial injury allows adhesion of platelets to the underlying extracellular matrix under the influence of von Willibrand factor (vWF) which is very important for binding of platelets to collagen and other surfaces.

Procoagulation Effects

Endothelial cells are activated to produce or synthesize tissue factor that activates the clotting cascade.

Antifibrinolytic Effects

Endothelial cells secrete inhibitors of plasmoinogen activator (PAIs) hence depresses fibrinolysis.

3.2. The Platelets

Platelets play a significant role in the process of blood clotting (haemostasis) through a number of reactions and functions. Platelets (thrombocytes) are the smallest cells formed elements from the fragments of large cells (**megakaryocytes**) found in the bone marrow. The platelets lack a

nucleus but are capable of amoeboid movement. They number approximately 130000 – 360000 per cubic millimetres of blood survive about five to nine days and are then destroyed by the spleen and liver.

Platelets constitute a major portion of the clot mass and the phospholipids in their cell membranes activate the clotting factors in plasma resulting in formation of fibrin that reinforces the platelet plug. Aggregated platelets release **serotonin** that stimulates constriction of blood vessels temporarily and effectively reducing blood flow to the injured area.

In the absence of vessel damage platelets are repelled from each other and from the endothelial lining of the blood vessels under the influence of **prostacyclin** (a prostaglandin derivative) produced by the endothelium. Damage to the vessel endothelial lining exposes the subendothelial tissues to the blood and triggers a series of reactions.

Functions of Platelets

The platelet functions include **adhesion**, **aggregation** and **release reactions**

Adhesion

Platelets undergo conformational changes and form pseudopodia. They stick to exposed collagen proteins, which have been coated with a protein (Von Willibrand factor) secreted by endothelial cells.

Aggregation

The platelets stick to collagen forming an aggregate mass of platelets and degranulate as the secretary granules release their products.

Platelet Release Reaction

The platelet granules breakdown releasing their products namely: – ADP (adenosine diphosphate), serotonin and thromboxane A_2 (a prostaglandin). Serotonin and thromboxane A_2 stimulate vasoconstriction. Exposed phospholipids on the platelet membrane activate clotting factors. ADP and thromboxane A_2 encourage platelet aggregation producing a platelet plug in the damaged vessel. This plug is strengthened by activation of plasma-clotting factors.

4.0 COAGULATION (CLOTTING)

4.1. Clotting Factors

There are twelve clotting factors numbered in roman numbers I – XIII according to their chronology of discovery (number VI is skipped). Different factors play different roles in the process of haemostasis.

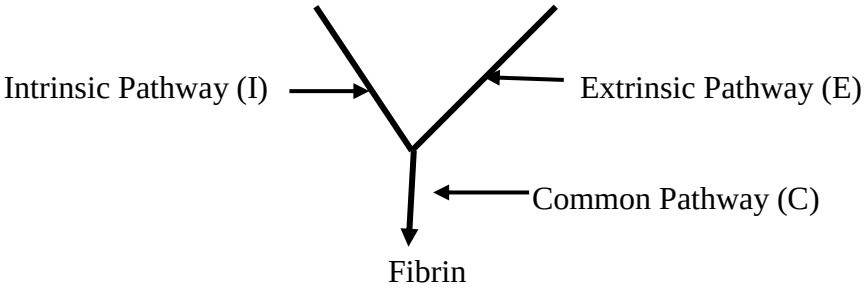
Table 3.2: Clotting Factors

Number	Name	Source	Function	Pathway
I	Fibrinogen	Plasma	Converted to fibrin	Common pathway
II	Prothrombin	Plasma	Enzyme	Common pathway
III	Tissue thromboplastin	Tissue	Co-factor	Extrinsic pathway
IV	Calcium	Plasma/ tissue	Co-factor	Intrinsic, extrinsic & common pathways
V	Proaccelerin/Labile	Plasma	Co-factor	Common pathway
VII	Proconvertin/Stable	Plasma	Enzyme	Extrinsic pathway
VIII	Antihaemophilic	Plasma	Co-factor	Intrinsic pathway
IX	Christmas (plasma thromboplastin component)	Plasma	Enzyme	Intrinsic pathway
X	Stuart power	Plasma	Enzyme	Common pathway
XI	Plasma thromboplastin antecedent (PTA)	Plasma	Enzyme	Intrinsic pathway
XII	Hageman	Plasma	Enzyme	Intrinsic pathway
XIII	Fibrin stabilizing		Enzyme	Common pathway

4.2. Coagulation (Clotting) Mechanism

Clotting is convert soluble fibrinogen into solid fibrin through a series of complex reactions via sequential activation of clotting factors. There are two main pathways – **extrinsic (tissue) pathway** and **intrinsic (blood) pathway** that result in conversion of fibrinogen into fibrin via an eventual common pathway.

Diagram 3.1: Clotting Pathway



The clotting mechanism has three essential steps

1. ***Formation of prothrombin activator***
2. ***Conversion of prothrombin to thrombin***
3. ***Conversion of fibrinogen into fibrin***

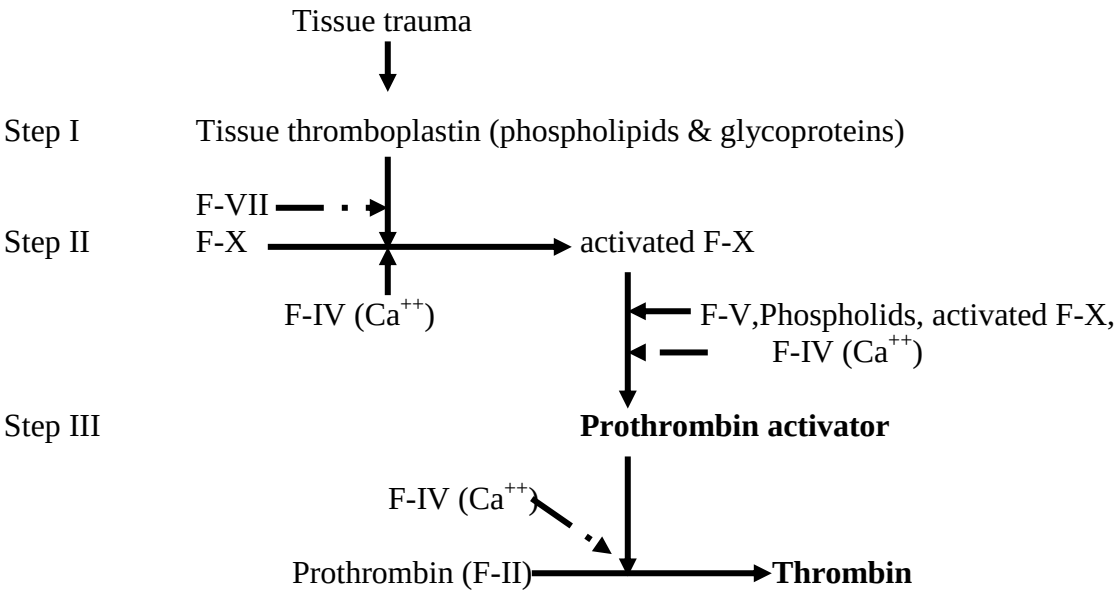
4.3. The Extrinsic Pathway (The Tissue System)

It is a shorter pathway that is activated by the injured tissues through Tissue factor III (thromboplastin) derived from damaged traumatized cells. This is enhanced by release of phospholipids from tissue membranes and glycoproteins, which form a proteolytic enzyme. The

end product of the extrinsic pathway is activated Factor X (Stuart-Power) and prothrombin activator, which convert inactive enzyme prothrombin into active enzyme **thrombin.**

The extrinsic pathway has three major steps: -
1. Release of thromboplastin from damaged tissues
2. Activation of Factor X by Factor VII and tissue phosphoilpids
3. Formation of prothrombin activator with the assistance of Factor IV (calcium) and Factor V.

Diagram 3.2: Diagrammatic Representation of the Extrinsic Pathway

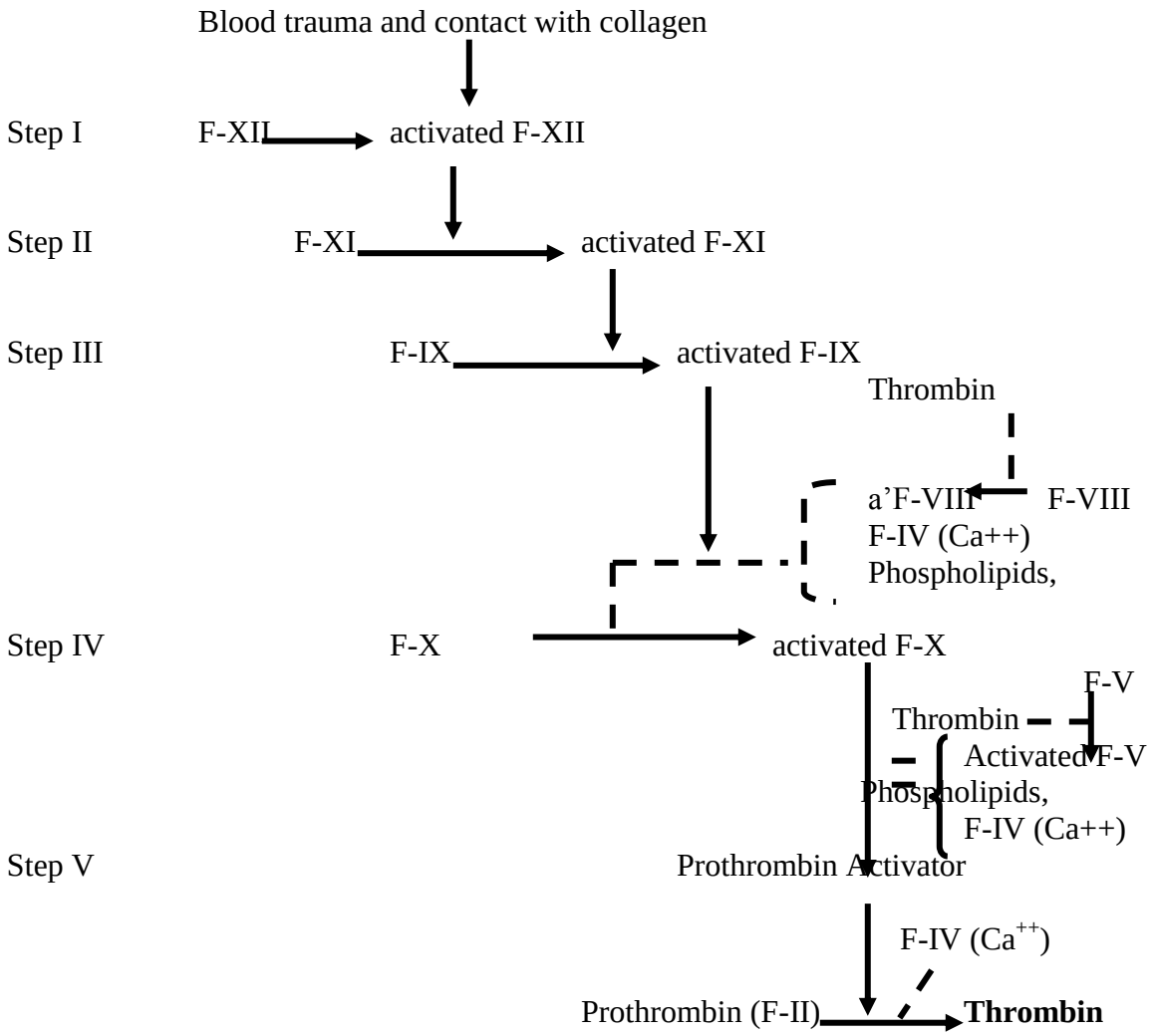


4.4. The Intrinsic Pathway (The Blood System)

It occurs without participation of factors released from the injured tissues. The intrinsic pathway is initiated by the exposure of plasma to negatively charged surfaces such as collagen at wound sites or glass of a test tube, which activates a plasma protein called Hageman (Factor XII), a protease (protein-digesting enzyme). It begins with activated F-XII, which triggers sequential activation of other clotting factors eventually resulting in conversion of the inactive enzyme, prothrombin into active enzyme **thrombin.**

The intrinsic pathway has five major steps: -
1. Activation of F-XII and release of platelet phospholipids by blood trauma
2. Activation of F-XI by activated F-XII
3. Activation of F-IX by activated F-XI
4. Activation of F-X by F-VIII, FIX. Phopholipids and F-IV (calcium)
5. Formation of prothrombin activator under influence of F-V and activated F-X, F-IV and phopholipids.

Diagram 3.3: Diagrammatic Representation of the Intrinsic Pathway



4.5. The Common (Final) Pathway

The common pathway involves the conversion of fibrinogen into fibrin. It begins at step II of the extrinsic pathway and step IV of the intrinsic one. The thrombin formed converts the soluble protein fibrinogen into fibrin monomers, which are joined together to produce the insoluble fibrin polymers that form a meshwork supporting the platelet plug. The clot contracts in 30 – 60 minutes times expressing most of the fluid (serum). The platelets are necessary for clot contraction as they become attached to fibrin bonding different threads together, release fibrin-stabilizing factor (Factor XIII) and activate the plasma actin and myosin molecules, which effect the clot contraction.

Diagram 3.4: Diagrammatic Representation of the Common Pathway

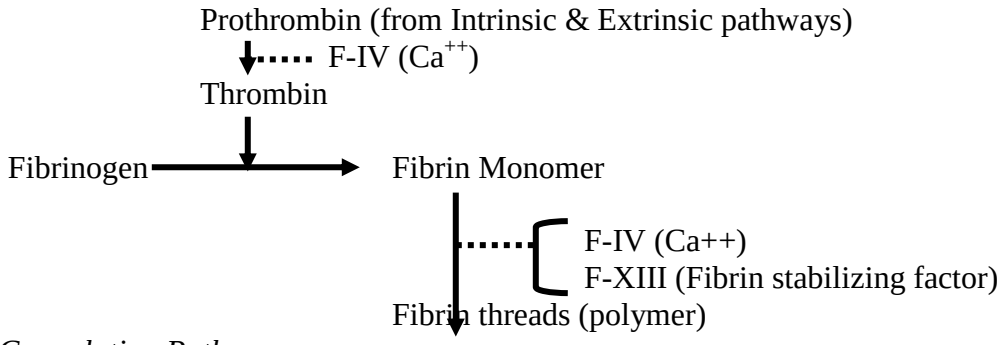
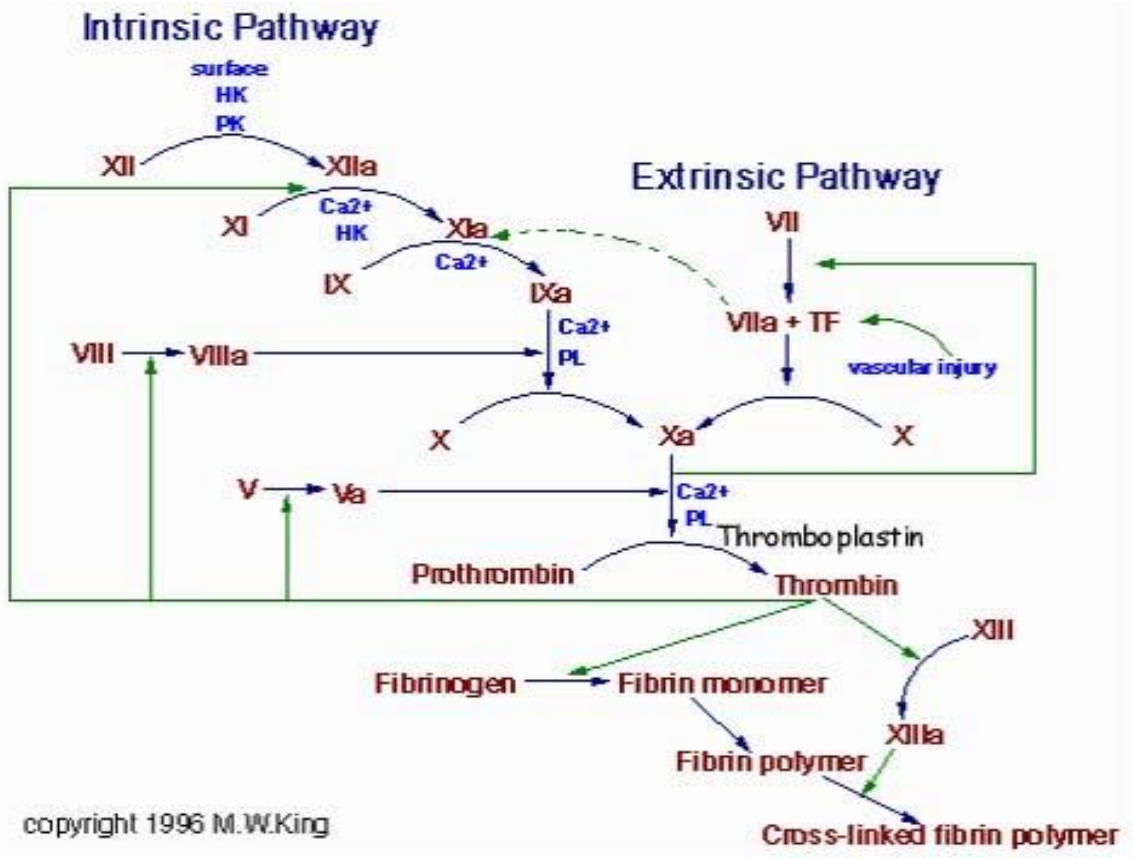


Diagram 3.5: Coagulation Pathways



The Fibrinolytic (Plasmin) System

The fibrinolytic system is essential for clot dissolution or removal. As the damaged blood vessel wall is repaired, activated factor XII promotes conversion of an inactive plasma molecule, pre-kallikrein into active form, kallikrein which catalyses conversion of inactive pro-enzyme plasminogen into the active molecule, plasmin. Blood plasma contains plasminogen with little amounts being synthesized by the vascular endothelium.

The following situations lead to increased levels of plasmin (due to increased plasminogen activator): -

1) Increased fibrin deposits
2) After surgery
3) Increased physical activity

4) Administration of vasopressin
5) High levels of catecholamines
6) Tissue plasminogen activator (TPA) – from genetic engineering technology
7) Streptokinase

Plasmin digests fibrin into split products, which are soluble promoting dissolution of the clot.

Disorders of Clotting

Table 3.3: Causes of defective blood clotting and the respective pathophysiology.

Category	Cause of Disorder	Pathophysiology
Acquired Disorders	1. Vitamin K deficiency	Inadequate formation of prothrombin and other clotting factors (F-VII, F-IX, F-X) in the liver
	2. Aspirin	Inhibits prostaglandin production resulting in defective platelet release reaction
	3. Anticoagulants a. Coumarins e.g. warfarin b. Heparin c. Citrate	 Antagonize action of vitamin K Inhibits activity of thrombin Combines with calcium inhibiting the activity of many clotting factors
	4. Advanced liver disease	Compromises formation of clotting factors – Factors II, VII, IX and X
Inherited Disorders	1. Haemophilia A (defective $FVIII_{AHF}$)	Recessive trait carried on X-chromosome; results in delayed formation of fibrin
	2. Haemophilia B (Christmas disease) – defective FIX	Recessive trait carried on X-chromosome; results in delayed formation of fibrin
	3. Von Willibrand disease (defective $FVIII_{VWF}$)	Dominant trait carried on autosomal chromosome; results in impaired ability of platelets to adhere to collagen in subendothelial connective tissues.

Task 2- Anticoagulants

Make a list of anticoagulants and state how they prevent coagulation.

DISSEMINATED INTRAVASCULAR COAGULOPATHY (D.I.C)

Introduction

Disseminated intravascular coagulopathy (D.I.C) is a bleeding disorder that results from excessive consumption of coagulation factors through formation of microthrombi throughout the microcirculation with subsequent activation of the fibrinolytic system. Fibrinolysis leads to production of fibrin degradation products (FDPs), which result in coagulation defects b inhibiting fibrin polymerisation. It may also be referred to as thrombohaemorrhagic disorder.

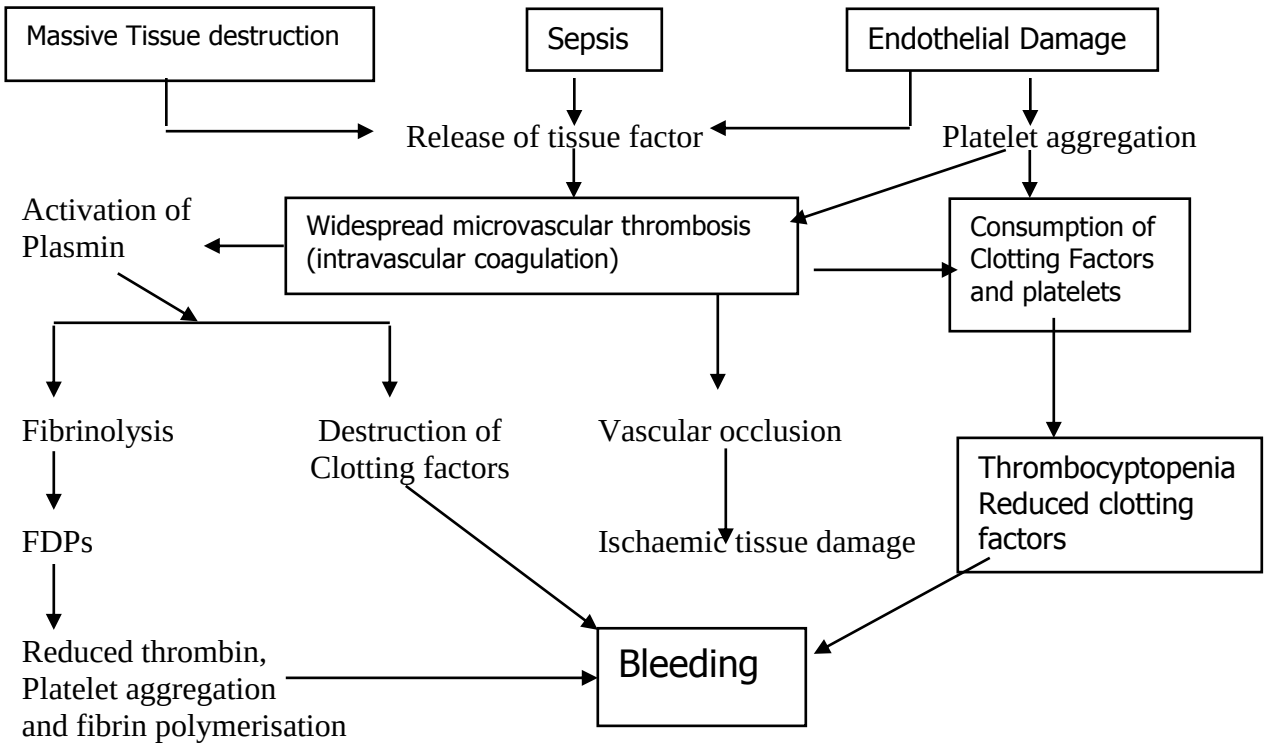
Causes of D.I.C

1. Obstetrics complications e.g. abruptio placentae, retained dead foetus, septic abortion, amniotic fluid embolism and toxaemia
2. Haemolytic transfusion reactions
3. Infections e.g. Gram negative sepsis, meningococcemia, malaria (falciparum)
4. Neoplasms e.g. carcinoma of the pancreas, prostate, lung and stomach; leukaemia
5. Massive tissue injury – traumatic, burns and extensive surgery
6. Miscellaneous- liver disease, acute intravascular haemolysis, vasculitis, shock and snake bites

Pathogenesis

1. Release of tissue factor or thromboplastic substances into the circulation
2. Widespread injury to endothelial cells

Diagram 3.6: Pathophysiology of D.I.C



Lesson 6: Blood Donation and Transfusion

Learning Outcomes

At the end of the session the learner should be competent to: -

1. Describe blood antigens and antibodies
2. Describe the genetics of blood groups
3. Outline the blood groups and grouping systems
4. Describe the process of blood donation
5. Identify indications for blood transfusion
6. Describe the process of blood transfusion
7. Describe the complications of blood transfusion

Blood Transfusion

1.0 INTRODUCTION

Blood transfusion medicine is both an art and science whose clinical benefits and patient harm require paramount considerations. The challenges of safety and availability of blood with economic overlay are of vital importance in blood transfusion medicine. The relationship between society and medicine is complex as health and longevity are entangled with power, economics, politics and media forces to give rise to conflicting imperatives.

Blood is a complex fluid consisting of different cells suspended in yellowish liquid called plasma. Whole blood contains a mixture of red cells (erythrocytes), white cells (leucocytes) and platelets (thrombocytes) suspended in plasma. The red cells contain haemoglobin whose primary function is to carry oxygen to the body tissues. Haemoglobin is a large complex molecule made up of iron-containing molecules called haem, which are attached to polypeptide chains called globin.

The white cells (leucocytes) are nucleated cells consisting of granulocytes (neutrophils, basophils and eosinophils), lymphocytes and monocytes. Their main task is body defence apparatus. Platelets play a significant role in the blood clotting mechanism. Serum is the fluid surrounding red cells, which have been allowed to clot. Plasma is the fluid surrounding the red cells that have been prevented from clotting.

Plasma contains many different proteins, chemical substances, clotting (coagulation) factors and numerous metabolic substances. Blood serves as a transport medium for carrying all its different components to different organs of the body.

2.0 BASIC BLOOD GROUP IMMUNOLOGY (IMMUNOHAEMATOLOGY)

2.1. Introduction

Red blood cells carry numerous surface complex carbohydrate antigens that account for the ABO grouping of blood while the Rh antigens are protein in nature. These antigens stimulate the B cells to synthesise IgM antibodies without the aid of the T cells that is to say the IgM antibodies are thymus-independent thymus dependent antigens give rise to IgG antibodies when T cells help

carbohydrate antigens shift from IgM to IgG formation. IgM results in intravascular haemolysis while IgG coat red blood cells leading to extravascular haemolysis.

An antigen is any substance recognized as foreign by the body, which stimulates the immune system to mount a response against it producing antibodies. An antibody is a protective protein produced by the immune response of an individual to stimulation by a foreign protein.

Antibodies are immunoglobulins (Ig) and found in the gammaglobulin part of plasma proteins. There are five categories of Ig: IgG, IgM, IgA, IgD and IgE. An immunoglobulin is an antibody molecule synthesized by plasma cells in response to antigenic stimulation and gammaglobins are a class of proteins that includes antibody molecule. Antibodies are formed of amino acid chains.

Erythrocyte blood group antigens are polymorphic, inherited, carbohydrate or protein structures located on the outside surface of the RC membrane. Blood group antigens are clinically in allogenic blood transfusions, maternofeotal blood group incompatibility and organ transplant. This is because exposure of erythrocytes carrying the antigen lacking on the RBCs of the recipient can elicit an immune response.

Blood groups can be used in genetic, forensic and anthropologic investigations due to the ease of detection by haemoagglutination and straightforward inheritance patterns.

Erythrocyte Membrane

The erythrocyte membrane consists of lipids, proteins and carbohydrates, which interact to form a dynamic and fluid structure. By weight, the ratio of proteins: lipids: carbohydrates is 49:43:8. The RBC membrane is a semi-solid structure with elastic and viscous properties that allow the survival of the RBC for 120 days with 75000 cycles and passages through the narrow veins and spleenic sinusoids without intracellular machinery to repair the damage.

Lipids

The lipids form a bilayer with hydrophobic tails on the inside and hydrophic polar head groups to either outside (extracellular) or the inside (cytoplasmic) surface. There are three types of lipids that make up the RBC membrane – phospholipids (50%), cholesterol (40%) and glycolipids (10%).

Proteins

Peripheral proteins form a meshwork under the bilipid layer, which is called the membrane skeleton that is fluidly and flexible. The membrane skeleton associates with the bilipid layer through transmembrane proteins, which carry many of the blood group antigens.

Carbohydrates

Carbohydrates are mainly found on the intracellular surface of the RBC membrane. They collectively form a negatively charged environment that largely keeps RBCs from adhering to one another and to the endothelium. Majority of the carbohydrates are attached to lipids and proteins.

Carbohydrates form the **glycocalyx**, which is a negatively charged barrier around the outside of the RBC membrane. This barrier keeps IgG antibodies from interacting with corresponding antigens

2.2. RBC Blood Group Antigens

Introduction

Recognition of blood group antigens begins with discovery of an antibody. There are 25 genetically discrete blood group systems recognised by the International Society for Blood Transfusion (ISBT) based on genes recognised by the International Society for Gene Nomenclature (ISGN). The ABO and Rh blood groups systems are the ones commonly used.

Inheritance

Most blood group antigens are encoded by genes on the autosomes with most of them being co-dominant. Several blood group antigens are not expressed or weakly expressed on foetal RBCs and do reach the adult levels at the age of 2 years. Cord RBCs express blood group D antigens just as the adults and show weak expression of antigens A and B.

Blood Group Antibodies

Blood group antibodies are classified according to the way of production: -

1. Naturally occurring antibodies - have a large molecular weight occur without antigenic stimulation e.g. IgM. They are cold antibodies causing agglutination of rbcs at $<37^{o}$ C.
2. Immune antibodies – Have Small molecular weight and respond to antigenic stimulation e.g. IgG. Are warm antibodies and cross-placental barrier.
3. According to reactions with rbcs in the laboratory - Complete antibody – agglutinate rbcs when they are suspended in saline and incomplete antibody – no agglutination in saline

The immunogenecity of blood group antigens is usually influenced by the ability to stimulate antibody production, which depends on: -

1. Antigen size
2. Complexity of the antigen
3. Dose of the antigen
4. Host HLA genotype

Exposures to antigens can occur during: -

1. Transfusion of products containing RBCs
2. Pregnancy
3. Exposure to microbes (immune antibodies that are naturally occurring)

Most carbohydrate based RBC antigens are T-cell independent and tend to elicit IgM responses while the protein based ones are T-cell dependent and induce IgM responses that progress to IgG processes. Detection and identification of blood group antibodies is done by the simple and less

expensive haemagglutination technique. Agglutination can be tested by direct and indirect method.

Let us briefly consider the IgG and Ig, .

IgG antibody has four chains (two light chains and two heavy) while IgM has ten light chains and ten heavy chains. IgG which have a life span of 60 – 70 days make up 73% of total Ig and they readily cross the placental barrier. They sensitize red blood cells. IgM comprise of 8% of Ig and do not cross the placental barrier. They have a large molecular weight and a life span of 10 days. They readily agglutinate red cells; activate the complement system causing haemolysis.

The ABO antibodies are naturally occurring, as they appear in the blood stream without ant any known antigenic stimulation.

2.3. ABO AND RELATED ANTIGENS

ABO blood group system was the first blood group system having been discovered in 1900 by Landsteiner who named the blood groups using the 1st two letters of the alphabet (A and RBCs not agglutinated were named C but were later called ohne A and ohne B). Ohne is a German word meaning without and then finally it was called O. in 1930 Nobel Prize winner for the discovery. ABO antigens are biochemically defined as carbohydrate structures on glycoproteins and glycolipids. There are 4 antigens namely A, B, AB and A1 (subgroup).

The antigens are synthesized in a stepwise fashion under the influence of glycosyl transferase enzymes. Antigens A and B have a similar structure but the differences arise from the terminal sugar at the 2nd carbon. Blood group O results from mutations in A or B alleles by deletion of the N terminal sugars. Blood group AB is as result of mutations in antigen A and B due to reduced activity of glycosyl transferases.

In 1914 –1917 methods for blood storage and preservation were introduced ushering in the blood bank environment.

2.4. ANTIBODIES

Anti-A and anti-B are found in the sera of individuals lacking the corresponding antigens. They are produced in response to environmental stimulants e.g. bacteria hence called "natural antibodies". Production begins at birth reaching the peak at 5-10 years and declines with increasing age.

The antibodies formed are mainly IgM as immune response induced by carbohydrates is thymus dependent. IgM antibodies activate the complement system. IgM plus high-density ABO antigens sites on the red blood cells results in life threatening reactions in ABO incompatible transfusion.

Haemolytic disease of the newborn (HDN) due to ABO antibodies is mild because: -

1. Placental transfer of antibodies is limited to IgG anti–A and B in maternal blood
2. Foetal ABO antigens are not fully developed
3. ABO tissue antigens provide additional targets for antibodies

ABO-HDN is often in non-group O infants of group O mothers because anti-A, anti-B and anti-A, B of group O mothers often having significant high IgG component.

3.0 BLOOD GROUPING

Blood group refers to a system of red blood cell antigens controlled by a locus having variable number of allelic genes A, B and O. Blood groups are genetically controlled with the locus for the allelic genes being on the long arm of chromosome 9. There are many methods of blood grouping namely: - ABO system, Rh, Lewis, Kell, P, Landsteiner/Weiner, Ii, MNS, Kidd, Duffy, Lutheran, Diego, ColtonKidd, Yt , Xg and Indian

THE ABO SYSTEM

Karl Landsteiner discovered the A, B and H antigens (ABH antigens) H antigen is the relevant carbohydrate structure present on blood group O red blood cells. It is classified according to the presence or absence of A or B antigens on the surface of the red blood cells and anti-A/anti-B in the serum. There are four blood groups based on the ABO system. Each parent donates the allelic genes A, B, O. The four groups result in four phenotypes (A, B, AB. O) and six genotypes (AA, AO, AB, BB, BO, OO).

Table 4.1: Blood Groups

Antigen	Antibody	Blood group	Receive from	Donate to
A, B	-	AB	All groups	AB
A	B	A	A, O	A, AB
B	A	B	B, O	B, AB
O	O	A, B	-	All groups

Rh Grouping

Landstainer & Weiner discovered the Rh blood grouping system in 1940. Three pairs of allelic genes C or c/D or d/E or e determine the Rh state. The locus of these allelic genes is on chromosome 1. The pairs are closely linked hence transmitted in sets of three – CDE, CDe, CdE, Cde, cde, cDE, cDe, and cdE. Individuals inherit a set from each parent gaining between 3 – 6 Rh antigens. The red cells which have D become Rh positive and those without D i.e. they have dd and c and e.

4.0 DONORS

The donors should healthy adults 16 – 65 years of age, The following are unsuitable donors: - Anaemic people, Hypertensives, Epileptics, Diabetics, TB patients, Pregnant mothers, Lactating mothers, Jaundiced individuals, Syphilis infection, Hepatitis, HIV/AIDS, Recently vaccinated, Drug addicts, Recently ill

There are basically three types of blood donors:

a) Family or family "replacement" donors
b) Paid commercial or professional donors
c) Voluntary non-remunerated (unpaid) donors.

4.1. Family of Family replacement donors

One or more donors from the patient's own family or community supply blood needed by a patient. The blood is added to the general pool in the blood bank and used as required. However, if is a directed donation then the blood is given to a named patient but this practice (directed donation) is discouraged by WHO.
Donors should not be told the identity of the recipients.

Advantages

1) Meet a need where voluntary donors are not available
2) Donors recognize the assistance and may become volunteer donors

Disadvantages

1) Search for the donors puts stress on the patients and relatives
2) Pressure on family members even when they are unsuitable donors
3) Relatives may be forced to get paid donors when they fail to get family members
4) May fail to meet the demand

4.2. Commercial or professional donors

Donors receive money or other rewards (which can be exchanged for money) for the blood they donate. They are usually motivated by what they receive rather than the wish to help other people. However, they can be persuaded to become voluntary non-remunerated donors

Disadvantages

1) Undermines the voluntary donor service
2) Poor donors may endanger their lives or those of recipients
3) Poor families may not be able to pay for blood transfusion

4.3. Voluntary non-remunerated donors

Voluntary non-remunerated donors are donors who give blood, plasma or other blood components of their own free will and receive no money or other form of payment. Their primary motivation is to help unknown recipients and not to obtain any personal benefit. The following items are not considered as payments or substitutes for money: -

1) Small tokens of recognition or appreciation such as badges or certificates
2) Reimbursement of direct costs of travel
3) Light refreshment immediately, during and after donation.

Advantages

1) Donors are not under pressure hence can meet the national criteria for low risk donors
2) Are willing to donate regularly
3) Are more likely to be free from transfusion-transmission infections because they have been educated about the importance of safe blood and have been screened severally.
4) Easily respond to appeals for blood donation.

5.0 BLOOD DONATION

Preparation

1. Take a medical history (Task – what do you want to know about the donor)
2. Establish any risks (How?)
3. Health check
   a. Blood pressure and Pulse rate
   b. Weight
   c. Evaluation of weight and height in relation to the age of the donor
   d. Physical assessment
   e. Donors last meal
4. Explain the procedure
5. Guarantee confidentiality
   a. During donor screening and blood collection
   b. Donor records
   c. Consent
   d. Published information
6. Take great care during venepunture and donation

Requirements and Materials

1. Blood bag
2. Anticoagulant preservative solution
3. Sphygmomanometer
4. 70% ethanol, sterile cotton gauze, adhesive tape
5. Emergency drugs and equipment (such as?)
6. Blood tubes for collection of blood

Technique

What is the technique of blood donation?

6.0 BLOOD COLLECTION & STORAGE

Blood is collected in plastic blood collection bags of 500 mls capacity containing acid citrate dextrose (ACD) anticoagulant, which stores blood for 21 days or citrate phosphate dextrose with adenine (CPD-A) capable of preserving blood for 28 days. Important substances in maintaining the viability of red cells are glucose an adenosine triphosphate (ADP).

Blood must always be stored at a temperature between $+2^{o}C$ and $+8^{o}C$. if blood is not stored at this temperature level; its oxygen carrying capacity is greatly reduced. This temperature range ensures moderate utilization of glucose, minimize growth of any bacteria and prevent freezing of red cells (which will haemolize if frozen).

Functions of Components in blood bag

1. Citrate – anticoagulant
2. Phosphate – buffer
3. Dextrose – metabolism and maintain red cell membrane
4. Adenine – generation of ATP (energy source)

Plasma

Fresh frozen plasma (FFP) is plasma that has been separated from whole blood within 6 – 8 hours of donation and has been rapidly frozen and maintained at a temperature of $-20^{o}C$ or lower. FFP is given to patients to help maintain clotting factors. Crystalloids and colloids are recommended for plasma volume replacement.

Plasma contains water, electrolytes, clotting factors and proteins mainly albumin. Most clotting factors are stable at refrigerator temperatures except for Factor VIII and Factor V, which are essential in clotting mechanism. These factors (VIII and V) deteriorate fast if plasma is not frozen at $-20^{o}C$ or less. In stored blood Factor VIII loses 50% activity in 24 hours and 100% activity in 72 hours. Platelets loose 50% of their haemostatic activity after 24 hours and the activity is zero after 72 hours.

Compatibility

Test for the ABO and Rh compatibility between the donors' red cells and the recipients' serum and do cross matching.

7.0 PROCESSING OF DONOR BLOOD

1. Blood grouping (ABO and Rh)
2. Screening and identification of unexpected antibodies
3. Screening for infections
    a. Hepatitis B surface antigen
    b. Anti-HCV antibodies
    c. HIV-1 and HIV-2 antibodies
    d. VDRL test
    e. Blood smear for malaria parasites

8.0 CHANGES OCCURRING IN STORED BLOOD

1. Loss of viability of red cells
2. Loss of ATP
3. Depletion of 2,3 DPH
4. Loss of granulocyte function
5. Decrease in blood pH
6. Increase in plasma potassium level
7. Decreased factor VIII
8. Formation of microaggregates

9.0 TRANSFUSION

Blood and blood products are used for various purposes. However, the three main reasons for blood transfusion are: -

1. *To correct anaemia (a low haemoglobin level)*
2. *To replace blood lost by bleeding, either during operation or because of an accident.*
3. *To replace other blood constituents, such as clotting factors.*

- Allogeneic transfusion – using blood donated by other donors

- Auto transfusion (autologus blood transfusion) – using blood donated by oneself
- Exchange transfusion

Task

- ✓ Explain the procedure for blood transfusion
- ✓ How do you determine the a mount of blood to transfuse
- ✓ Describe the patient care during transfusion

Rate of transfusion

In non-bleeding patients – 2-3 ml/Kg/hr but reduced to 1 ml/Kg/hr in patients at risk of developing fluid overload.

Table 4.2: Red Cell Derivatives

Component	**Description**	**Indications**
Whole blood	Contains all components of blood	Correct deficiency of oxygen carrying capacity e.g. massive haemorrhage and exchange transfusion.
Red cell concentrates (packed cell volume)	Remove plasma and retain the red cells	Red cell deficit
Washed red cells	Red cells are washed using isotonic saline solution to remove plasma proteins	Prevent allergic reactions Prevent anaphylaxis
Frozen red cells	Remove plasma and retain the red cells then freeze them	Autologous storage Rare donor unit storage

10.0 TECHNIQUE OF TRANSFUSION

What is the technique of blood transfusion?

11.0 COMPLICATIONS OF BLOOD TRANSFUSION

A. Transfusion reactions
   1. Haemolytic reactions
      a) Acute haemolytic transfusion reactions (AHTR)
      b) Delayed haemolytic transfusion reactions (DHTR)
   2. Non-Haemolytic reactions
      a) Febrile reactions
      b) Allergic reactions

B. Infectious Complications (Infections)
   1. Bacterial contamination (sepsis)

2. Blood itself - Retroviral infections, HIV/AIDS, Hepatitis A, B, C, D, E, G, Herpes virus infection, CMV, EBV, Human Herpes Virus 8 infection, Parasitic, Malaria, Toxoplasmosis, Leishmaniasis, Trypanosomiasis, Spirochete infections, Syphilis and Yellow fever

C. Allergic reactions/Anaphylactic reactions
D. Circulatory overload (Hypervolaemia)
E. Respiratory distress
F. Metabolic Derangements
   1. Hypothermia
   2. Electrolyte toxicity – citrate, potassium, magnesium, calcium
G. Iron overload
H. Air embolism
I. Thrombophlebitis
J. Other adverse effects

Transfusion Reactions

A transfusion reaction is any unpleasant reaction that occurs as a consequence of infusion of blood or one of its components. Acute reactions occur during transfusion or within several hours after transfusion while delayed ones occur days (haemolytic reactions), months or years (infections) after the transfusion.

HAEMOLYTIC TRANSFUSION REACTIONS

Haemolytic transfusion reactions are caused **by immune-mediated destruction (haemolysis)** of red blood cells. The haemolysis can be classified according to time of reaction (**acute or delayed**) or site of destruction (**intravascular or extravascular**). This gives four categories of reactions – acute intravascular, acute extravascular, delayed intravascular and delayed extravascular.

1. Acute Haemolytic Transfusion Reactions (AHTR)

Acute haemolytic transfusion reaction can be defined as rapid destruction of blood cells immediately after or within 24 hours of transfusion. This is more common with transfusion of whole blood or RBCs but transfusion of platelets, fresh frozen plasma (FFP) or other plasma derived factors containing antibodies incompatible with the recipient's RBCs may cause AHTR.

Acute Intravascular Reactions

These are reactions that occur within minutes of transfusing incompatible red blood cells (with the ABO antigens) into a patient possessing the corresponding antibodies (ABO) e.g. transfusing "A" red cells into an O recipient who has circulating "A" antibodies.

Acute Extravascular Reactions

The antigen bound on IgG forming complexes that are destroyed by IgG receptors in the spleen. It is a mild reaction that does not destabilize the state of the patient. It is prudent to monitor renal and haemostatic function.

Pathophysiology

This follows transfusion of whole blood or RBCs that are immunologically incompatible with antibodies pre-existing in the recipient. Antigens react with antibodies forming antigen-antibody complexes causing complement and cytokine stimulation.

Features

Common features

Fever, chills/rigors, chest pain, hypotension (due to anaphylaxis secondary to presence of anaphylatoxins), facial flushing, tachycardia , shortness of breath/dyspnoea, bronchospasms
Pallor, jaundice, diffuse bleeding, haemoglobinuria, renal failure (due to necrosis of renal tubules)

Other features

Dizziness, anxiety, abdominal pain, back and flunk pain, nausea and vomiting, diarrhea and altered state of consciousness

Management

1. Stop the transfusion immediately
2. Assess the patient
3. Recheck the identity of blood units and patient
4. Take blood samples from the patient
5. Supportive management
    a. Maintain IV line to resuscitate hypotension - IV fluids at 3000 ml/M^2/day, Crystalloids
    b. Hydrocortisone
    c. Antihistamines
    d. Support cardio-respiratory system
    e. Diuretics e.g. Frusemide (Lasix)
6. Check compatibility
7. Monitor creatinine and blood urea nitrogen (BUN)

2. Delayed Haemolytic Transfusion Reactions (DHTR)

DHTR is usually recognized 3 to 10 days after transfusion of blood that is serologically incompatible. This is more common I patients who have been previously allo-immunised by transfusion or pregnancy but antibodies were not detected.

NON-HAEMOLYTIC TRANSFUSION REACTIONS

Febrile Reactions

Introduction

Febrile nonhaemolytic transfusion reaction is defined as a temperature rise of at least 1^o C occurring with or without chills in association with transfusion or shortly thereafter (up to 4 ours)

in the absence of a recognized cause. They occur due to cytotoxic or agglutinating antibodies in the patient's plasma reacting against antigens present on transfused donor lymphocytes, granulocytes and platelets. The reaction is mediated by cytokines from macrophages, monocytes, granulocytes and lymphocytes. They result in production of prostaglandins PGE_2 that stimulates the thermoregulatory centre of the hypothalamus to produce fever.

Features

- Nausea and vomiting, Fever, Chills, Rigors, Shivering

Management

1. Stop transfusion
2. Check compatibility
3. Antipyretics – aspirin, NSAIDS, paracetamol/acetaminophen (avoid aspirin in patients with less platelets as compromises their function)
4. Antihistamines
5. Blood cultures
6. IV fluids

Allergic Transfusion Reactions

Allergic transfusion reactions are commonly due to infusion of **plasma proteins**. It is believed to be associated with IgG and IgE antibodies. Allergic reactions constitute a large proportion of all transfusion reactions (45%).

An anaphylactic reaction when plasma-containing IgA is transfused to patients with IgG anti-A antibodies. This reaction leads to activation of the kinin system releasing bradykinin that enters the circulation causing vasodilatation, hypotention, pain and cutaenous flushing without fever or chills. It is worse in patients taking ACE inhibitors since ACE degrades bradykinin.

Allergic transfusion reactions can be classified according to reaction types into three main categories with an overlapping spectrum.
1. Uncomplicated allergic reactions of localized or diffuse urticaria
2. Anaphylactoid allergic reactions
3. Anaphylactic allergic reactions

Anaphylactic reactions have a high potential for adverse reactions while an uncomplicated allergic reaction consists of urticaria. Severe hypotension, fever, chills, bronchospasms or dyspnoea, nausea, vomiting, diarrhoea and urticaria characterize anaphylactic transfusion reactions. These severe reactions may occur after infusion of a very small volume (< 10 mls) of blood product. Anaphylactoid reactions are generally less severe than anaphylactic ones. They commonly occur in individuals with anti-IgA

Differentials
1. ACE inhibitor transfusion-related resections
2. Transfusion related acute lung injury (TRALI)
3. Myocardial infarction
4. Pulmonary embolism

Management

1. Stop transfusion
2. IV fluids
3. Antihistamines
4. Adrenaline
5. Supportive therapy

Table 4.3: Differential Diagnosis of Acute Transfusion Reactions

Reaction type	Signs and symptoms
Acute intravascular haemolytic	Fever, chills, dyspnoea, hypotension, tachycardia, flushing, vomiting, back pain
Acute extravascular haemolytic	Fever, jaundice, reduced post-transfusion haematocrit
Febrile reaction	Fever, chills
Allergic (mild)	Urticaria, pruritis, rash
Anaphylactic	Dyspnoea, bronchospasm, hypotension, tachycardia, shock
Hypervolaemic	Dyspnoea, tachycardia, hypertension, headache, jugular venous distension (raised JVP)
Septic	Fever, chills, hypotension, tachycardia, vomiting, shock

Skin-Restricted Allergic Reactions

These are reactions that occur in up to 3% of all transfusions characterized by a localized or confluent red, raised rash or itching or both (collectively called urticaria). Lesions are classified as uncomplicated when there are no accompanying features of asthma-like attacks and difficulty in breathing.

Post-transfusion Purpura (PTP)

PTP consists of profound thrombocytopenia occurring 1 to 2 weeks occurring as a result of antibodies against donor platelets antigens, which the recipient lacks.

Transfusion-Related Acute Lung Injury (TRALI)

This occurs during or within 4 hours of transfusion and is characterized by symptoms of respiratory distress, which manifest radiographically by the presence of bilateral pulmonary infiltrates. Other features include chills, fever, increased respiratory rate, cough and tachycardia. TRALI results from donor antibodies directed against white blood cell antigens (HLA). The resulting agglutination due to antigen-antibody reaction produces agglutinins, which are then trapped in the pulmonary circulation and release toxic substances and injury with pulmonary oedema.

Transfusion Transmitted Diseases

BACTERIAL CONTAMINATION (SEPSIS)

Contamination of blood with bacteria possess grave risks to the recipients. Bacteria gain entry into the blood bag during venipuncture or component preparation. Different bacteria require different environment for optimal growth. Gram-negative bacteria e.g. Pseudomonas, Yersinia, Enterobacter and Flavobacterium are associated with contaminated refrigerated blood. Platelet concentrates stored at room temperature may harbour Salmonella and Staphylococcus.

Features

Fever, Rigors, Skin flushing, abdominal cramps, Myalgias, D.I.C, Renal failure, Circulatory collapse, Cardiac arrest

Management

1. Stop the transfusion
2. Monitor vital signs
3. Culture the untransfused blood
4. Give appropriate treatment – broad-spectrum antibiotics
5. IV fluids

Table 4.5: Sources and Mechanism of bacterial Contamination

Source	**Organisms**
Donor bacteraemia	Yersinia eneterocolitica, Campylobacter jejui, Staphylococcus aureus, Borrelia, Salmonella cholerasuis, Trepanoma pallidum
Blood collection	Staphylococcus epidermidis, s. aureus, diphtheroids, enterococci
Blood bag manufacture	❑ Pseudomonas cepacia
Blood bag damage	❑ Serrata species
Blood processing	Pseudomonas aeruginosa

BLOOD ITSELF

1) Retroviral infections, HIV/AIDS
2) Hepatitis A, B, C, D, E, G
3) Herpes virus infection
4) CMV, EBV
5) Human Herpes Virus 8 infection
6) Malaria
7) Toxoplasmosis
8) Leishmaniasis
9) Trypanosomiasis
10) Spirochete infections, Syphilis and Yellow fever

Retroviral infection

HIV1 and HIV2 viruses that cause AIDS can be transmitted in blood during transfusion.

Precautions/Screening

- Take note of the window period (16 days) i.e. the period from HIV infection to seroconversion by checking for HIV-1 p24 antigen markers
- Polymerase chain reaction (PCR) detects HIV genomic signals 11 days after infection.
- ELISA test and Western blot test
- Check CD4+ and CD8+ cells.

Hepatitis

Hepatitis A, B, C, D, E and G can be transmitted during blood transfusion. Hepatitis C is a major cause of transfusion infections.

Cytomegalovirus (CMV) Infection

CMV is a large enveloped double stranded DNA herpes virus, which resides intracellular in leucocytes. It causes pneumonitis, hepatitis, gastroenteritis, retinitis and other inflammatory conditions in immunosuppressed individuals.

Patients at risk for transfusion-transmitted CMV

1. Infants with low birth weight
2. Children born to IV-infected mothers
3. Neonates receiving extensive transfusion support (exchange transfusion)
4. Seronegative patients infected with HIV
5. Seronegative women requiring intrauterine transfusion
6. Seronegative patients on chemotherapy
7. HIV infected persons

Other herpes viruses that can be transmitted through blood transfusion include Epstein-Barr virus and Human Herpes virus 6, 7 and 8.

Malaria

Malarial parasites can be transmitted during transfusion because Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae maintain viability in red cells stored at 4^{o}C and platelet concentrates stored at room temperature. Malaria is not transmitted by RBC-free components e.g. plasma and cryoprecipitate. The incubation period is 7 – 50 days (average 20 days).

Features

Chills, Fever, Spleenomegally, Fatigue, Nausea and vomiting, Headache, Diarrhoea

Management

- Antimalarial drugs

Syphilis

Trepanoma pallidum, the spirochete causing syphilis loses viability after 7 days' storage at refrigerated temperatures.

Circulatory Overload (Hypervolaemia)

Circulator overload occurs in up to 1 in 100 transfusions. Circulatory overload results from acute rapid expansion of the patient's intravascular volume exceeding the capacity of the cardiovascular system through rapid and excessive transfusion. Rapid transfusion in a patient with euvolaemia without active bleeding produces no benefits but harm. Patients with poor working cardiac and pulmonary systems cannot tolerate rapid transfusion.

Features

- Severe sudden headache, Cough , Dyspnoea, Tachycardia, Tachypnoea, Congestive cardiac failure

Management

1. Stop transfusion or reduce rate of transfusion
2. Reduce blood volume – diuretics, phlebotomy

Respiratory Distress

Respiratory distress syndrome (RDS) occurs due to aggregation of debris of dead platelets, granulocytes and fibrin strands that form in blood during storage. Occurs concurrently with sepsis and hypotension. Using filters in the transfusion sets has greatly reduced RDS.

Metabolic Derangements

Introduction

Metabolic derangements are most commonly encountered in neonatal or rapid, large volume transfusions. These metabolic effects may interact synergistically causing a variety of manifestations. The metabolic derangements include: - hypothermia, citrate toxicity, hypocalcaemia, hypomagnesia and hyperkalaemia.

Hypothermia

Hypothermia occurs with rapid infusion of large quantities of refrigerated blood (1-6^{o}C). Blood should be warm before transfusion. However, over warming blood causes thermal injury and produce haemolysis, DIC or shock.

Hyperkalaemia

Hyperkalaemia is a rare problem associated with massive transfusion. However, development of hypokalaemia is of greater concern. In stored blood, potassium leaks from the red cells to the extracellular fluids, after infusion the red cells reverse this trend restoring potassium levels, and the citrate is metabolised to bicarbonate the blood becomes alkalotic contributing to hypokalaemia.

Hypocalcaemia

Occurs due rapid infusion of citrated blood but in patients with normal liver function citrate is metabolized to bicarbonate. Features of hypocalcaemia range from circumoral[3] paraesthesis to

[3] Extending around the mouth

frank tetany. Severe citrate toxicity is rare even with massive. High levels of calcium are associated ventricular fibrillation and cardiac arrest.

Hypomagnesia

Hypomagnesia results from chelating of magnesium to citrate. It is a rare occurrence.

Citrate Toxicity

Citrate is used in the preservative solution used in storage of blood where it functions as an anticoagulant by chelating with calcium and interfering with the clotting cascade.

Haemosiderosis (Iron Overload)

Iron overload is an uncommon complication that occurs after long periods of time in patients who are transfused very often for chronic disease.
One millilitre of red cells contains 1 mg or iron meaning a unit of blood with 250 ml red cells will contain 250 mg of iron, 4 units of blood 1 gram the amount normally stored in the bone marrow. Males and non-menstruating women loose 1 mg iron/day.

Heamosiderosis, which is accumulation of excessive tissue stores of iron, occurs in repeated transfusion therapy in extravascular haemolysis e.g. sickle cell disease and thalassaemia where iron is not lost from the body but recycled. Excess iron is stored in parenchymal cells resulting in cell death and eventual organ failure.

Air Embolism

Air embolism results from poor handling of the processes of transfusion. Use of plastic blood bags has greatly reduced the risks of air embolism. The air emboli lodges in the right ventricle preventing blood entering the pulmonary circulation resulting in acute cyanosis, pain, cough, shock, arrthymias and death if severe.

Lesson 7: Shock 1 – Causes, Pathophysiology and Types of Shock

Learning Outcomes

At the end of the lesson the learner should be competent to: -

1. Define basis terms
2. Describe the causes of shock
3. Classify shock
4. Describe the pathogenesis of shock
5. Describe body response mechanisms to shock
6. Describe the types of shock

1.0 INTRODUCTION

Shock is reduced tissue perfusion (a condition arising from reduced tissue perfusion). It is a state of hypoperfusion resulting from reduction in either cardiac output or effective circulating blood volume. Shock is a clinical state associated with generalized failure of tissue perfusion. This reduction results in hypotension causing impaired tissue perfusion and cellular hypoxia. It can also be described as a state of acute circulatory failure due to disparity of blood volume and vascular bed causing depression of vital body functions or a medical emergency characterized by a reduction in the effective circulatory blood volume and blood pressure. Shock is the final common pathway of numerous fatal events.

Shock results in depression of vital body functions due to reduced cardiac output and effective circulating blood volume culminating in progressive cardiovascular collapse characterised by hypotension, hyperventilation, clouding of consciousness and eventually Oliguria.

The cardinal consequences of shock occur as a result of two mechanisms of loss of effective circulating that cause tissue and cell damage and the reactive changes that take place in the circulation. This produces the shock syndrome that comprises reduced cardiac output, hypotension, impaired tissue perfusion and cellular hypoxia.

When shock occurs, the body operates a number of regulatory or compensatory mechanisms, which are geared to minimizing the functional disturbances. In a prolonged state of shock, these mechanisms are bound to fail leading to interference with cellular functions and death. This therefore calls for all the necessary therapeutic intervention to aid the body responses counter the disturbances.

2.0 HAEMODYNAMIC HOMEOSTASIS

Consider the following factors that influence the impact of shock on body functions

1. **Cardiac output (CO)** - Cardiac output is the volume of blood pumped by each ventricle per minute and averages 5.6 litres in an average adult. Cardiac output [CO] mls/min = stroke volume (mls/min) X cardiac rate (beats/min)
2. **Stroke volume (SV)** - This is the volume of blood ejected from the ventricles per beat and averages 70 – 80 mls/beat. Is regulated by End-diastolic volume (EDV) preload which is the

volume of blood in the ventricles at the end of diastole, total peripheral resistance which is the frictional resistance or impedance to blood flow in arteries and contractility an after load that reflects the strength of ventricular muscles.

3. **Cardiac rate (heart rate) -** Cardiac rate is a function of the beats per minute that is regulated by the Sino atrial node (SAN), sympathetic nervous system and the vagus nerve.

4. **Venous return** - This is return of blood via veins to the heart. The rate at which the atria and ventricles are filled with venous blood depends on the total blood volume and venous pressure
5. **Blood volume** – is regulated by the kidneys
6. **Blood pressure** (BP) = CO X PR and is regulated by hormones, the kidneys and the nervous system

3.0 CAUSES OF SHOCK

1. Reduction of blood volume (Hypovolaemia)

    a. Exogenous losses
        1) Severe blood loss/Haemorrhage which can be externally or internally from **trauma (**wounds, surgical operations and organ rupture), **Obstetric** - ante-partum haemorrhage (APH), post-partum haemorrhage (PPH) and ectopic pregnancy and **medical disorders** - bleeding peptic ulcer, bleeding oesophageal varices and rupture of aneurysm
        2) Plasma loss
        3) Extensive vascular exudation – burns, dermatitis, peritonitis
        4) Fluid and electrolyte loss
            - Alimentary tract – gastroenteritis, dysentery, intestinal obstruction.
            - Diarrhoea and vomiting
            - Renal - excessive diuretic therapy, diabetic coma

    b. Endogenous losses
        1) Infections Bacteria – streptococcus, clostridia, pneumococcal, shigella
        2) Septicaemia leads to peripheral trapping of blood volume due to abnormal vasodilatation
        3) Anaphylaxis

2. Cardiogenic
    a. Inadequate cardiac output - severe congestive cardiac failure (CCF), massive myocardial infarction
    b. Obstruction of major vessel e.g. pulmonary artery and aorta

3. Obstructive
    a. Obstruction to outflow e.g. pulmonary embolus
    b. Restricted cardiac filling (Inadequate venous return to the heart)
        - Mechanical obstruction to venous return - inferior vena cava compression by tumours and gravid uterus, portal vein thrombosis and iatrogenic positive pressure ventilation (PPV).
    c. Cardiac tamponade

4. Distributive Causes
    a. Primary or neurogenic shock (Sequestration)
        - Severe painful stimuli – trauma, extensive burns, severe multiple fractures, perforation of abdominal viscera and crushing of testis
        - Overwhelming emotional trauma
        - Traumatic damage to the brain
        - Vasovagal syncope
    b. Vascular dilatation
        - Excess morphine, general anaesthesia and barbiturates
        - Spinal anaesthesia
        - Hypotensive drugs
        - Histamine and other vasotoxins
    c. Arteriovenous shunting
    d. Maldistribution
        1) Sepsis /Bacterial toxins
        2) Anaphylactic reactions
        3) Animal toxins – snakes, bees, scorpions, spiders
        4) Physical agents (extreme cold, very high altitudes, extreme hyperpyrexia, electrocution
        5) Sudden abdominal decompression e.g. ascitic tapping
        6) Orthostatic hypotension

4.0 PATHOGENESIS OF SHOCK

Introduction

Irrespective of the type of shock the pathogenesis pivots on two basic mechanisms of reduced effective circulating blood volume and anoxia (reduced oxygen supply to the cells). Patients with septic shock have hyperdynamic circulation due to peripheral vasodilatation, pooling of blood and increased vascular permeability that result in reduced effective circulating volume.

Mechanisms

Reduced effective circulating volume

Reduction in effective circulating blood volume can result from actual blood loss (hypovolaemia) and decreased cardiac output without actual blood loss (normovolaemia). Reduction in effective circulating volume falls under three mechanisms: -

1. Hypovolaemia – a fall in cardiac output due to reduced blood volume
2. Cardiogenic – a fall in cardiac output as a result of inadequate cardiac function “pump failure”.
3. Vascular mechanisms
    a. Pooling of blood due to loss of vasomotor tone, increased vascular permeability and slowing of blood flow
    b. Disseminated intravascular coagulopathy

Tissue hypoxia

Reduced effective circulating blood volume results in reduction in cardiac output subsequently reducing the supply of oxygen to tissues and organs leading to hypoxia and anoxia thus shock ensue.

Diagram 7.1: Pathogenesis of shock

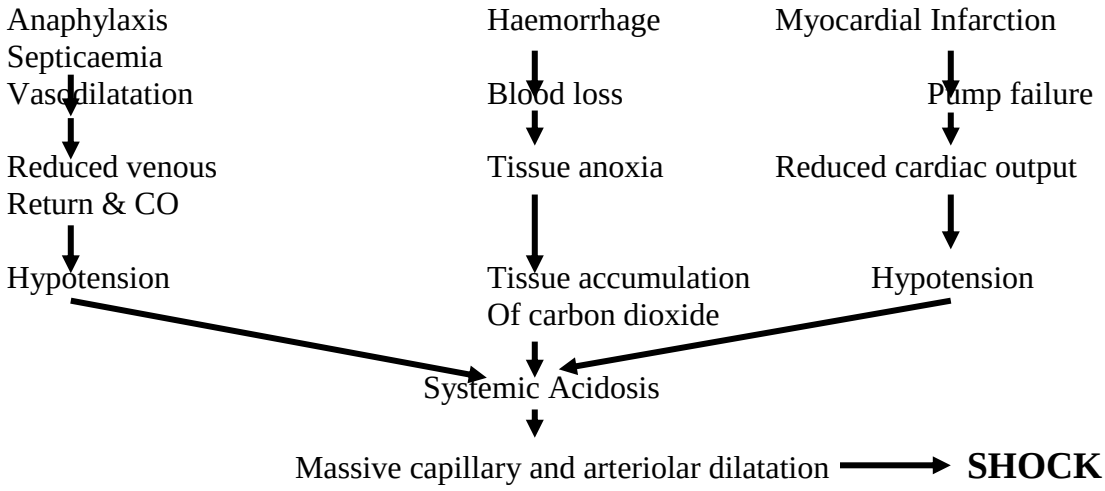
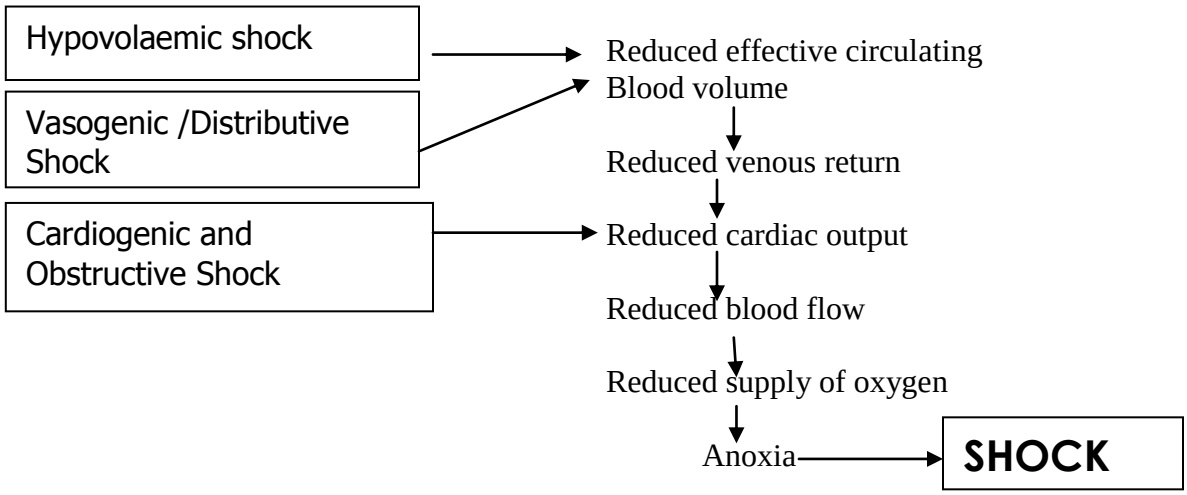


Diagram 7.2: Events in aetiology and pathogenesis of shock



5.0 PHYSIOLOGIC RESPONSE TO SHOCK

The body's physiological response to shock involves three (3) stages namely: -

A. The immediate response
B. Delayed response
C. Recovery phase

5.1. The Immediate Response

The main aim of this phase of response is to restore the blood pressure through fluid retention mechanisms and increase in peripheral resistance via a number of mechanisms. The immediate response involves the kidney, catecholamines and hormones.

Catecholamines

The release of catecholamines from the adrenal medulla causes vasoconstriction. There is also improved myocardial contractibility.
Contraction of the spleen under the influence of epinephrine leads to release of stored blood increasing the blood volume.

The kidney

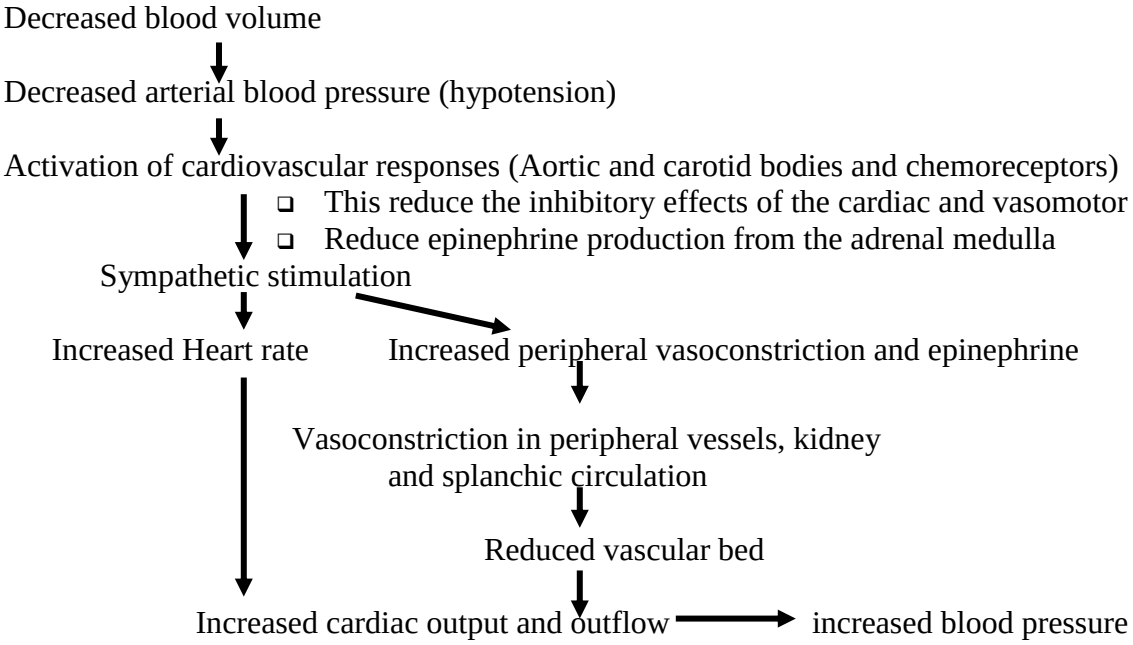
Reduced renal perfusion stimulates the juxtaglomerular apparatus (JGA) causing activation of the Renin-angiotensin-AVP system, which results in vasoconstriction and sodium and water retention.

Hormones

There are several hormones that are released by the body and perform different functions
1. Pituitary Hormones - Adrenocorticotrophic hormone (ACTH) and AVP – causes sodium and water retention
2. Cortisol - Cause fluid retention as well as antagonizing insulin
3. Glucagon - Raise blood sugar levels

If blood loss is severe, these adaptive mechanisms are inadequate leading to dilatation of peripheral capillaries, which in turn cause a reduction in venous return and blood eventually pools at the periphery.

Diagram 7.3: Immediate physiologic response



5.2. Delayed Response

Delayed phase lasts up to three days when haemodilution and haemoconcentration takes place. The patient has an increased respiratory rate due to anoxia, reduced haemoglobin and reduced circulation. There are increased adrenal steroids which increase gluconeogenesis.

5.3. Recovery Phase

The recovery phase entails replacement of lost cells (tissue and blood [RBCs, WBCs]) and plasma proteins. The period of this phase depends on severity of blood loss, state of the bone marrow and the patient's nutritional reserves in case of haemorrhagic shock. In the other forms of shock it will depend on elimination of the causative mechanism and ability of body control mechanisms to take full control of restoration of circulation.

6.0 CLASSIFICATION OF SHOCK

There are three main classes of shock: -

1. Hypovolaemic shock
2. Cardiogenic shock
3. Vasogenic shock
    a. Neurogenic shock
    b. Septic sock
    c. Anaphylactic shock

Hypovolaemic Shock

Hypovolaemic shock is due to reduction in blood volume as a result of haemorrhage, loss of plasma and loss of fluids and electrolytes. Hypovolaemic shock may be compensated (reversible) or decompensated (irreversible)

Cardiogenic Shock

Cardiogenic shock results form inefficiency of the heart function due to myocardial infarction, pulmonary embolism and myocarditis.

Vasogenic Shock

In vasogenic shock there is peripheral vasodilatation that increases the vascular bed alongside increased permeability of capillary walls and capillary atony and dilatation. The end result is accumulation of blood in the peripheral system hence low cardiac output. Vasogenic shock can be sub classified as bacteraemic/endotoxic shock, anaphylactic shock and neurogenic shock.

7.0 TYPES OF SHOCK

7.1. HYPOVOLAEMIC SHOCK

Hypovolaemic shock occurs doe to loss of circulating fluid volume (whole blood, plasma and water) leading circulatory fluid pressure and volume deficits.

Causes

1. Blood loss/haemorrhage
2. Plasma loss
3. Fluid and electrolyte loss

7.2. HAEMORRHAGE (HAEMORRHAGIC SHOCK)

Introduction

This results from massive loss of whole blood. Loss of 10% blood volume (500 mls) causes no disability as there is no change in blood pressure and cardiac output and the volume is replaced within 1 – 2 days. Loss of 20% blood volume causes significant hypovolaemia leading to shock. If the blood loss is 45% there is marked reduction in blood pressure and cardiac output reaching zero.

Causes

1. Traumatic – Wounds, Trauma, Surgical operations, Traumatic rupture of the liver, spleen, kidney
2. Obstetric/gynaecology - Ante-partum haemorrhage (APH), Post-partum haemorrhage (PPH), Ectopic pregnancy, Abortions, Uterine fibroids, Malignancy, During child birth
3. Medical disorders
    a. Gastro-intestinal tract - Peptic ulcer disease (P.U.D), Oesophageal varices, Malignancy
    b. Cardiovascular system –m Rupture of aneurysms
    c. Genital urinary tract - Haematuria
    d. Bleeding disorders e.g. Haemophilia

Plasma loss

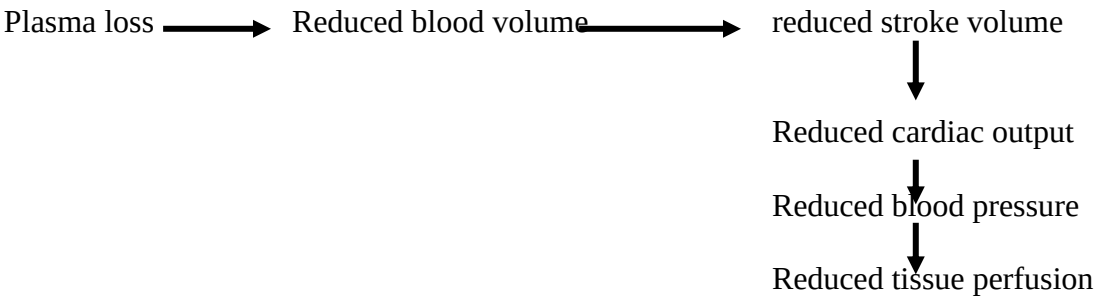
Plasma loss arises from loss of plasma fluid.

Causes

1. Extensive vascular exudation – Burns, Dermatitis, Peritonitis
2. Anaphylaxis

When there is a plasma loss the blood pressure control mechanisms are activated in order to maintain the blood pressure.

Diagram 7.4: Effects of plasma loss



Fluid & Electrolyte Loss

Leads to dehydration due to extensive/profuse fluid loss

Causes

Profuse sweating, Extensive G.I.T loss - Diarrhoea & vomiting and Upper G.I.T suctioning, Diabetes insipidus, Ascites, Lack of adequate fluid intake, Diuretic phase of acute renal failure (ARF), Addison's disease, Hypoaldosteronism, Osmotic diuresis, Injudicious use of diuretics

Burns

Causes of shock in burns: -

a) Fluid loss
b) Loss of plasma proteins
c) Haemorrhage - Occurs due to destruction of blood vessels (trauma); Clots that blocked blood vessels in the burnt surface promote platelet aggregation and activation of Factor XII causing ischaemic necrosis and eventually disseminated intravascular coagulopathy (D.I.C) that leads to haemorrhage.
d) Sepsis will result from destruction of the natural barrier, toxins from the burnt surface injure intestinal capillaries allowing intestinal bacteria to access the systemic circulation, secondary bacterial infection and and necrotic tissues and ischaemia
e) Neurogenic/pain

Changes seen in Hypovolaemic shock – Compensatory mechanisms

1. Early changes

   The early changes are acute hypovolaemia resulting in reduced systemic central venous pressure (CVP) and a fall in blood flow into the right atrium effectively lowering the venous return (VR) and stroke volume (SV) and subsequently the cardiac output and blood pressure.

2. Haemodynamic changes

   The haemodynamic changes trigger off central and peripheral receptors that in turn lead to sympathetico-adrenal stimulation resulting in increased release of catecholamines (epinephrine and nor-epinephrine) by over two hundred fold (Over 200 times).

   Epinephrine increases: -
   1) Cardiac output and peripheral resistance
   2) Efficiency of muscular contraction
   3) Respiratory rate and dilates the respiratory pathways
   4) Rate of glucagons breakdown increasing blood glucose level
   5) Rate of fatty acids release from fats

   Norepinephrine
   1) Causes generalized vasoconstriction
   2) Has similar effects as epinephrine

3. Reduced renal perfusion (RAA mechanism)

A fall in renal perfusion leads to rennin production. Rennin converts angiotensinogen to angiotensin I which in turn is converted to angiotensin II which is a powerful vasoconstrictor and influences release of aldosterone that causes sodium and water retention improving the overall situation of blood volume.

4. Effects of catecholamines and angiotensin

   Catecholamines together with angiotensin will cause constriction of arterioles and venules in the skin, splanchic area and most of the other tissue improving total peripheral resistance and eventual restoration of blood pressure.

   There is increased tone of the systemic veins causing an apparent reduction in central venous pressure leading increased right atrial filling thus increasing the cardiac output and blood pressure.

   Take note that:

   The heart and central nervous system tissue perfusion remains normal due to auto-regulatory mechanisms. Their small blood vessels do not contract in response to noradrenaline.

5. Erythropoietin production - There is increased erythropoietin production due to hypoxic states in the body.

6. ACTH - Increased adreno-cortico-trophic hormone (ACTH) increases gluco-corticoids that maintain capillary integrity and reduce the effects of the mediators of inflammation.

7. 2,3 Diphosphoglycerate

   2,3 Diphosphoglycerate interacts with haemoglobin (Hb) to promote release oxygen.

8. Prostaglandins

   Show mixed effects such as vasoconstriction and retardation of platelet aggregation.

9. Complement system

   Activation of the complement system leads to cell lysis and promote leucocyte dysfunction leading to respiratory distress syndrome (RDS).

Clinical Signs of Hypovolaemic Shock

- Low cardiac output
- Low central venous pressure (CVP)
- Increased systemic vascular resistance
- Inadequate tissue perfusion
  - Skin – cold, pale, blue, slow capillary refill
  - Kidneys – Oliguria, anuria
  - Brain – confusion and restlessness

- Increased sympathetic tone - tachycardia, narrow pulse pressure/low pulse volume and sweating
- Blood pressure – low
- Metabolic acidosis

7.3. CARDIOGENIC SHOCK

Introduction

Cardiogenic occurs as result of acute circulatory failure due to sudden reduction in cardiac output without actual reduction of blood volume (normovolaemia).

Causes

1. Deficient emptying of the heart – that pump failure when the heart is ineffective in pumping out blood e.g. Myocardial infarction, Rupture of the heart, Cardiomyopathy, , toxins, Infections, Congenital heart disease, Rheumatic heart disease (RHD) and Cardiac arrhythmias (tachycardia and bradycardia).
2. Deficient filling of the heart chambers (reduced venous return) e.g. cardiac tamponade, pericardial effusion and mediastinal shift.
3. Obstruction to outflow of blood from the heart e.g. pulmonary embolism.

Mechanism

- The heart is unable to contract effectively leading to heart failure.
- Extensive myocardial damage lead to reduced cardiac output due to impaired myocardial contractibility with loss of functional myocardium. Pump failure occurs when 50% of the myocardial tissue is non-functional.
- Cardiac rhythm abnormalities interfere with coordination of pump function.
- Reduced Venous Return due to reduced blood flow into the heart as a result of conditions that squeeze the heart impairing venous inflow.

Compensatory Mechanisms – changes seen

Compensatory mechanisms set in to restore perfusion by increasing the heart rate and blood pressure. The decrease in stroke volume, cardiac output and perfusion are worsened by autonomic nervous system (ANS) responses because: -

1. Increased heart rate leads to increased oxygen demand and reduced diastolic refilling time thus ischaemia
2. Vasoconstriction increase the pressure overload on the ventricular function
3. Selective vasoconstriction shunts blood to the heart but away from the other organs with a possibility of organ/tissue damage.

Signs indicative of Cardiogenic shock

1) Hypotension
2) Pulmonary oedema
3) Decompensation – ascites, oliguria/anuria
4) Cold/diaphoretic skin

5) Pallor
6) Reduced or altered sensorium
7) Abdominal distension due reduced bowel sounds
8) Bradycardia
9) Raised JVP
10) Pulsus alternans
11) "Gallop" rhythm
12) Increased CVP
13) Low cardiac output
14) Increased systemic vascular resistance

8.0 OBSTRUCTIVE SHOCK

Clinical signs

1) Elevated JVP
2) Pulsus paradoxicus
3) Muffled heart sounds
4) Kussmaul's sign (JVP rises on inspiration) in cardiac tamponade
5) Signs of pulmonary embolism
6) Low cardiac output
7) Increased CVP
8) Increased systemic vascular resistance

9.0 VASOGENIC (VASCULAR) SHOCK

Introduction

Vasogenic shock results from a low resistance in the blood vessels or a maldistribution of the blood volume. There is marked increase in vascular capacity or dilatation relative to the amount of circulating blood volume. The circulating capacity to accommodate volume is increased.

The initiating agents, that is – vasomotor failure and potent vasodilator substances, hamper the compensatory mechanisms. The sympathetic vasomotor stimulation is inadequate due to the nature of the primary defect and the RAA and ADH secretion is impaired.

Causes

1. Vasomotor centre depression (neurogenic shock)
2. Sepsis (septicaemic shock)
3. Anaphylaxis (anaphylactic shock)

10.0 NEUROGENIC SHOCK

Introduction

It is also referred to as spinal shock. It results from loss of vasomotor tone, which induces generalized arteriolar and venous dilatation causing reduction in peripheral resistance and thus hypotension and reduced tissue perfusion. The blood pools in the storage or capacitance vessels

and the splanchic organ capillaries further reducing the effective circulating blood volume. The vasomotor tone is maintained by the action of the vasomotor centre (VMC) in the medulla and the sympathetic nervous system.

Causes

1. Head injury
    a. Direct
    b. Indirect – cerebral oedema and increased intracranial pressure
2. Brain stem depression - General anaesthesia and Drug overdose –n opiates, barbiturates, tranquillisers
3. Spinal injury
4. High spinal anaesthesia
5. Syncope/fainting

11.0 SEPTICEAMIC SHOCK

Introduction

It is a severe profound condition of generalized vascular collapse secondary to systemic infection mainly by the gram-negative organisms. Septicaemic shock is related to release of endotoxins from the bacterial cell wall hence it is also called endotoxic/toxic shock. Gram-positive organisms do produce exotoxins. Septic shock is associated with three patterns of response i.e. hyperdynamic (acute infection picture), normodynamic (transient period) and hypodynamic (irreversible)

Causes

Gram-negative septicaemia (endotoxic shock) will occur in infections with E. coli, Proeteus, Klebsiella, Pseudomonas, bacteroids and bacilli e.g. haemophilus, cholera, salmonella (typhoid fever). Gram-positive septicaemia (exotoxic shock) due to infections by streptococci, pneumococcus is less common.

Pathogenesis of septicaemic shock

1. Endotoxin release
2. Capillary damage
3. Macrophage activity

Endotoxin release

The endotoxins are released by the bacterial wall and necrotic bowel. The toxins cause fever, abnormal clotting, hypotension as a result of massive vasodilatation and elevation of compliment levels. They also activate histamine, lysosomal enzymes, bradykinin and serotonin, which compromise the integrity of the capillary walls causing damage.

Damaged Capillary

Damaged capillary allows leakage of plasma causing a further reduction in blood volume, thus cardiac output and blood pressure are likewise reduced.

Macrophage activity

The macrophages activate the complement system, coagulation factors and prostaglandins, which mediate shock.

Clinical Signs of Septicaemic Shock

Pyrexia and rigors, Hypothermia (rare), Vasodilatation – warm peripheries, Nausea/vomiting, Rapid capillary refill, Bounding pulse, Hypotension, Jaundice , Low CVP, Low systemic vascular resistance and Cardiac output – increased or maintained by tachycardia

12.0 ANAPHYLACTIC SHOCK

Introduction

Anaphylactic shock is the most drastic acute developing and rapid progressing shock that can result in death within one hour of onset. Anaphylactic shock is induced by antigen-antibody (Ag-Ab) reaction (type I hypersensitivity reaction). It is initiated by action of IgE that binds to the mast cells and basophils releasing substances such as histamine, bradykinin and prostaglandins that mediate shock.

Pathogenesis

The histamine dilates blood vessels, constricts respiratory smooth muscles and increase vascular permeability and this reduces the peripheral resistance and blood volume effectively reducing the blood pressure hence reduced tissue perfusion (shock). Bradykinin causes vasodilatation and increases in vascular permeability while the prostaglandins potentiate vascular permeability.

Clinical features (Signs & Symptoms)

Hypovolaemia due to capillary leak, Signs of profound vasodilatation – warm peripheries and low blood pressure (hypotension), Tachycardia, Erythema, Urticaria, Angio-oedema, oedema of the face, pharynx and larynx, Pulmonary oedema, Pruritis, Fever, Dyspnoea with voice hoarseness, stridor, broncho-spasms, wheezing, Oliguria, Cool moist skin, Pallor
Nausea and vomiting, abdominal cramps and diarrhoea, Cyanosis, Anxiety, Low systemic vascular resistance, Low CVP, High cardiac output and History of allergy

Lesson 8: Progression/Stages, Outcome & Complications of Shock

Learning Outcomes

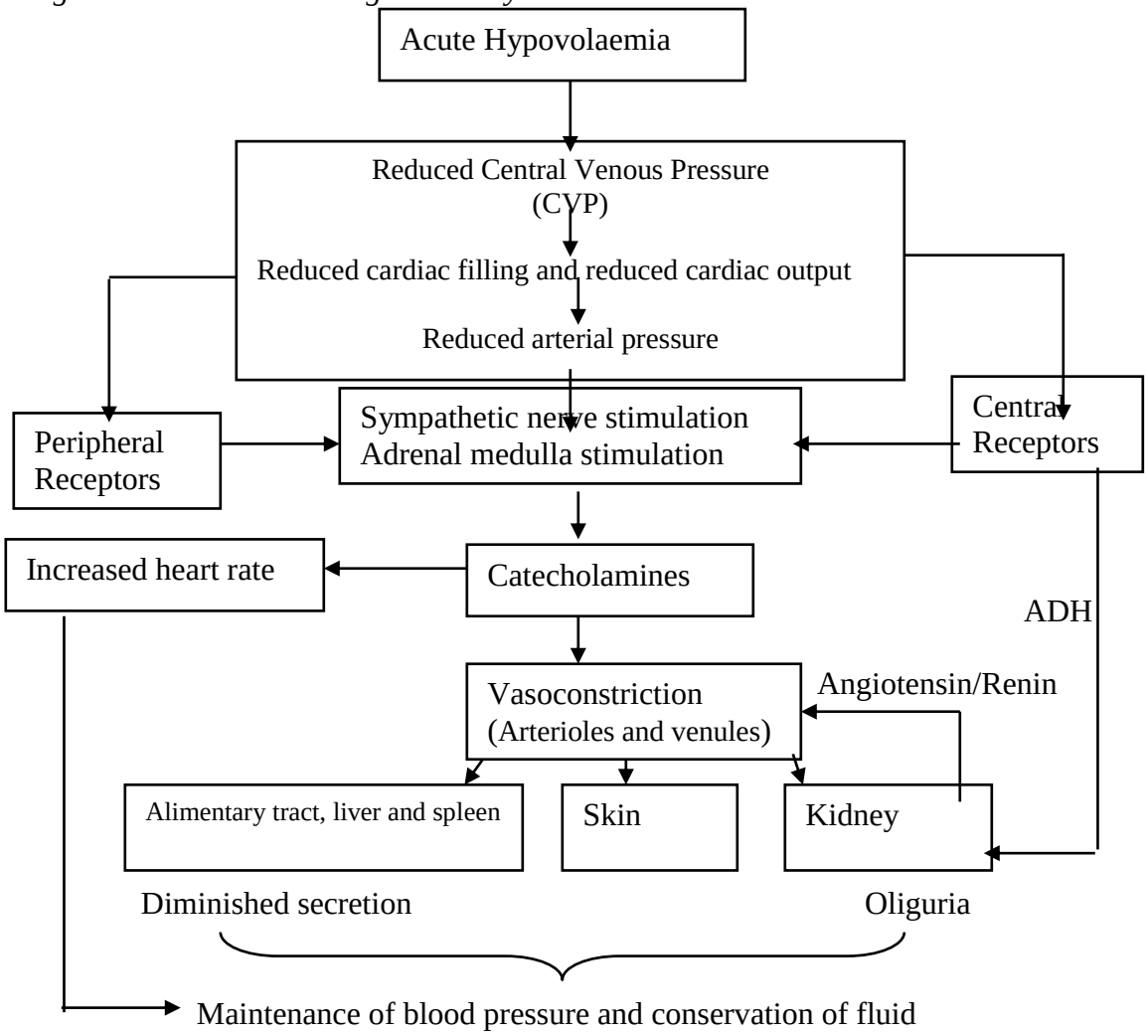
At the end of the lesson the learner should be able to: -

1. Describe the stages and progression of shock
2. Predict the outcome of shock
3. Describe the complications of shock
4. Outline important investigations in shock

1.0 INTRODUCTION

Initially the body attempts to counter the effects of shock by setting in compensatory mechanisms in order to restore cardiac output, blood pressure and effective circulating blood volume. If the mechanisms work competently the body functions are restored but if the situation persists or worsens life threatening functional and structural changes will occur in the body causing multiple organ failure and eventually death.

Diagram 8.1: Reactive changes in Early Shock



2.0 PROGRESSION OF SHOCK – STAGES OF SHOCK

Deterioration of circulation in shock progresses in three stages namely: -

1. ***Non-progressive (initial, reversible compensated, early) shock***
2. ***Progressive decompensated shock.***
3. ***Decompensated (irreversible) shock.***

Diagram 8.2: Stages of Shock

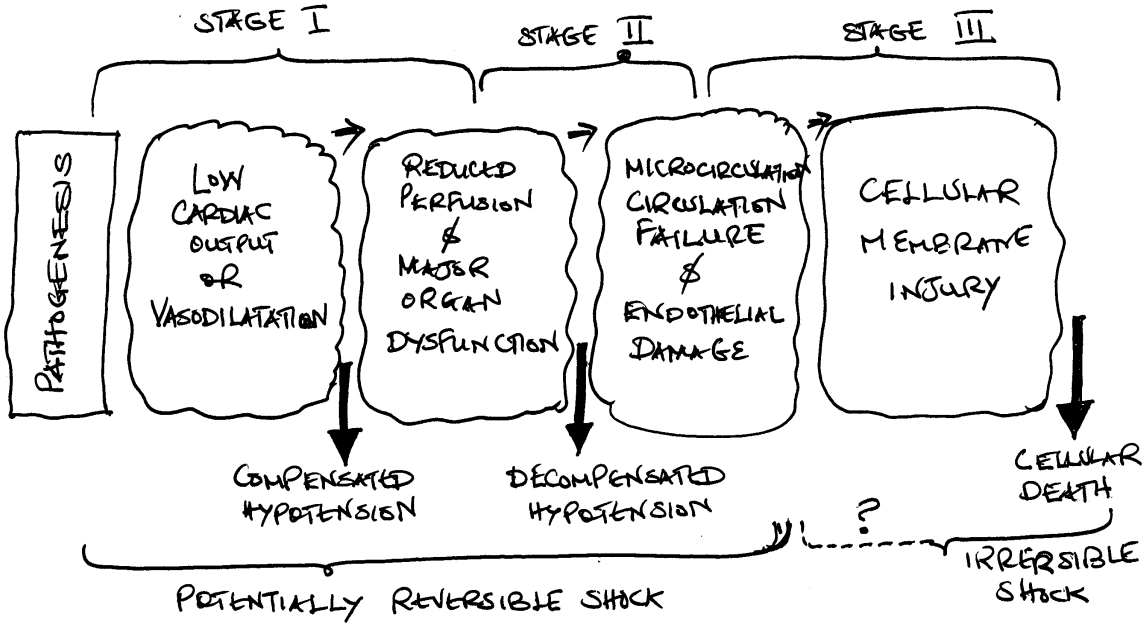


Table 8.1: Mechanisms and Effects of the stages of shock

Stage	Pathogenesis	Effects
I - Initial shock	❑ Effects of baroreceptors ❑ Release of catecholamines ❑ RAA activation ❑ ADH release ❑ Sympathetic stimulation	❑ Peripheral vasoconstriction ❑ Cool clammy skin ❑ Tachycardia ❑ Fluid Conservation
II - Progressive shock	❑ Anaerobic glycolysis ❑ Lactic acidosis ❑ Lower pH	❑ Reduced cardiac output ❑ DIC ❑ Mental confusion ❑ Reduced urine output
III - Irreversible shock	❑ Persistent vasoconstriction ❑ Vasodilatation ❑ Increased permeability ❑ Myocardial ischaemia ❑ Cerebral ischaemia ❑ VDM	❑ Brain – death ❑ Lungs - Respiratory distress ❑ Heart - Myocardial infarction ❑ Kidney – acute tubular necrosis ❑ Liver – necrosis ❑ Spleen – hyperplasia ❑ Stomach – ulcer ❑ Intestines - necrosis

2.1. Stage I: Early stage – Compensated/Non-progressive Shock

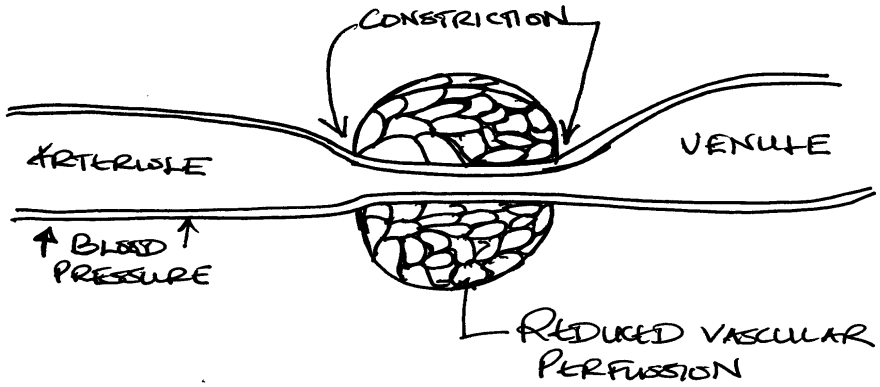
Introduction

This is the early or initial phase of response to the injury when several physiological compensatory mechanisms are stimulated to restore blood volume and blood pressure. The body makes an attempt to maintain adequate cerebral and coronary blood supply by redistributing blood in the whole body in order to adequately perfuse and oxygenate vital organs – the brain and heart. The circulations in the brain and heart are protected by autoregulatory mechanisms hence they don not respond to the generalized vasoconstriction

It involves:-

1) Autonomic nervous system and vasomotor centre
2) Activation of the RAA system (Kidney)
3) Increased secretion of ADH (vasopresin)

Diagram 8.3: Compensatory phase of shock

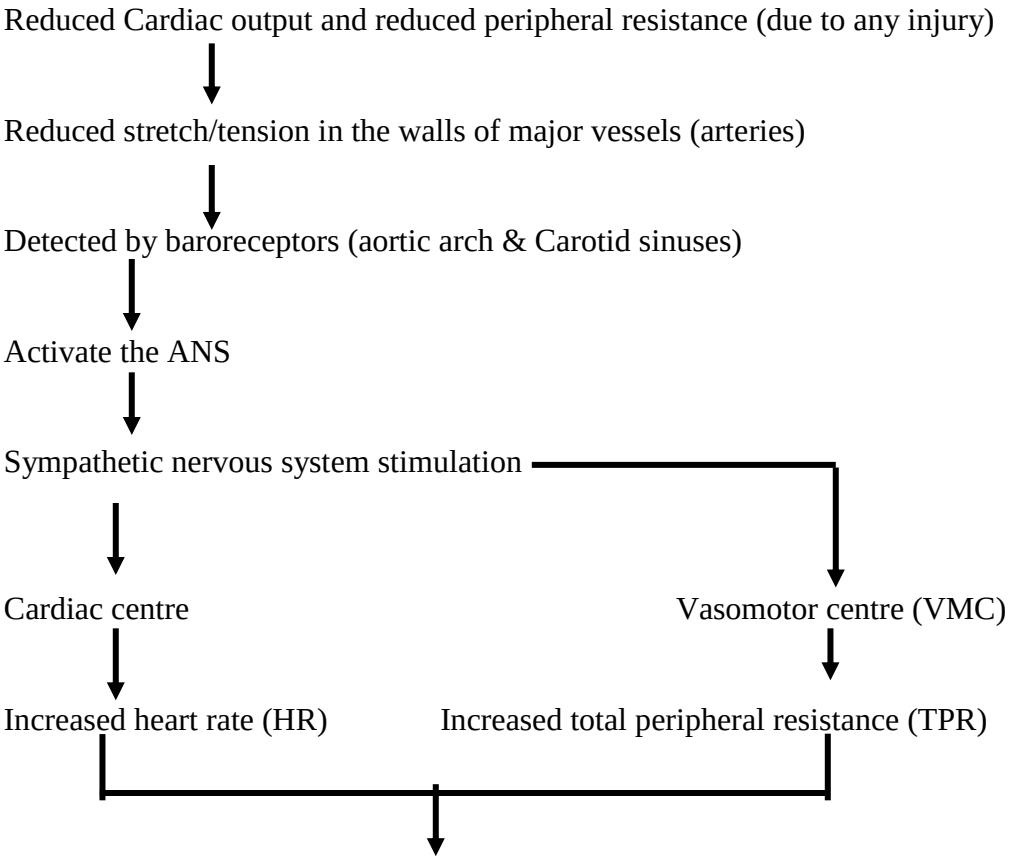


The Autonomic nervous system

This occurs in several second to minutes and assists the body restore blood pressure, cardiac output and eventually tissue perfusion. Widespread vasoconstriction occurs in response to reduced blood flow (hypotension) and tissue anoxia, which activate neural and hormonal factors e.g. **baroreceptors**, **chemoreceptors**, **catecholamines** and **rennin**. It is a protective mechanism that brings about increased peripheral resistance, increased heart rate and increased blood pressure.

Vasoconstriction at both the arteriole end (increases blood pressure) and the venule resulting in diminished vascular perfusion of tissues and tissue hypoxia. Increased sympathetic activity causes constriction of both precapillary arterioles and post capillary venules helping to maintain systemic blood pressure. Hydrostatic pressure falls within the capillaries allowing fluid to mobilized from the extravascular space into the intravascular compartment. As the blood pressure rises circulation is usually restored.

Diagram 8.4: Diagrammatic Representation of ANS stimulation



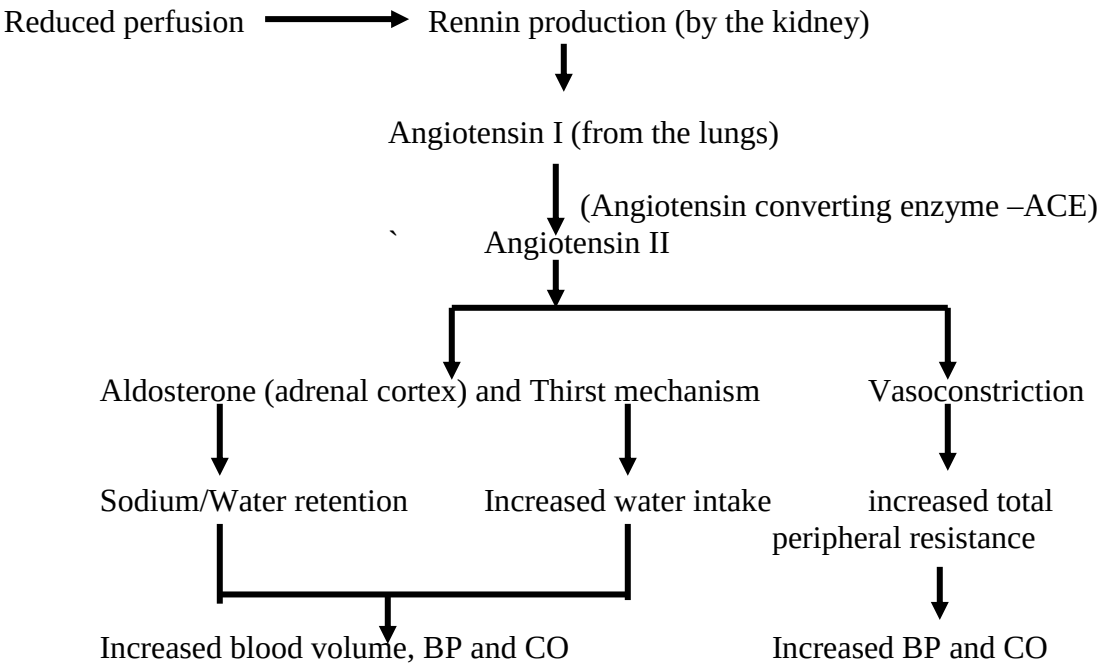
Activation of the RAA system (Kidney)

The kidney conserves body fluid restoring blood volume and hence venous return and cardiac output. This is made possible by release of aldosterone from the hypoxic kidney, release of ADH due to decreased effective circulating blood volume, reduced glomerular filtration rate (GFR) due to arteriolar constriction and shifting of tissue fluid into plasma because of lowered capillary hydrostatic pressure hypotension). This follows reduced renal perfusion secondary to reduced blood pressure and cardiac output.

ADH (Vasopressin) Release

Increased secretion of ADH (vasopressin) due to reduced pressure in the atria, aortic arch and carotid sinuses leads to increased water conservation and together with vasoconstriction restores the blood volume, blood pressure, and cardiac output and tissue perfusion.

Diagram 8.5: Diagrammatic representation of RAA mechanism



In the initial stage the body conserves fluid to compensate for the actual loss of volume of blood through release of aldosterone from the hypoxic kidney, vasopressin due to decreased effective circulating blood volume, reduced glomerular filtration rate (GFR) due to arteriolar constriction and shifting of tissue fluids into plasma because of lowered hydrostatic pressure (hypotension).

Clinical Features (Signs & symptoms)

1) Patient is awake/alert
2) Anxious
3) Increased heart rate/Tachycardia
4) Normal blood pressure (reduced if SNS function is reduced)
5) Skin is pale, moist and cool
6) Pupillary dilatation
7) Increased shallow respiration
8) Reduced urine output
9) Thirst
10) Hyperactive bowel
11) Muscle weakness
12) Reduced reflexes

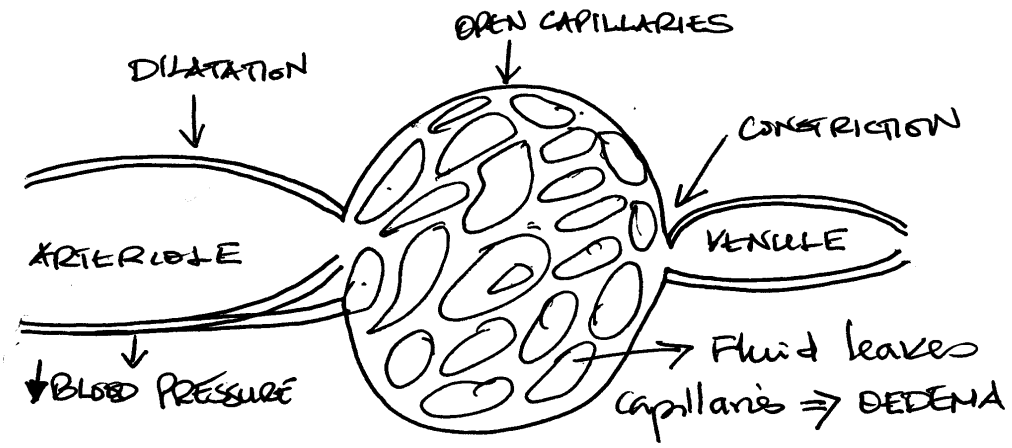
2.2. Stage II – Progressive (Advanced) shock

This is s a decompensated shock because the compensatory mechanisms deployed in stage I to maintain tissue perfusion of the vital organs fail. There is worsening clinical picture of the patient due to the effects of prolonged tissue and organ hypoperfusion and the ensuing ischaemia.

During this stage the body is unable to restore the blood volume, venous return, cardiac output and blood pressure hence the state of shock persists. It is made worse by other pre-existing risk factors such as cardiac and pulmonary diseases.

There is dilatation of the precapillary arteriole sphincters occurs due to accumulation of metabolites (such as lactic acid and carbon dioxide) and release of vasoactive substances whereas the postcapillary venules which are very sensitive to hypoxia remain constricted and unresponsive to vasoactive amines. Blood is sequestrated within the dilated capillary bed and fluid is forced into the extravascular spaces causing interstitial oedema, haemoconcentration and increased blood viscosity. This leads to gross reduction in vascular volume and tissue perfusion with marked tissue hypoxia.

Diagram 8.6: Failing Compensatory mechanisms



Effects of Low BP and Hypoxia

At the beginning of the process of shock all body tissues suffer hypoxia except the brain and heart. This state of hypoxia usually triggers a series of viscous circles, which make the state of shock worse.

In advanced shock patients can demonstrate impaired perfusion of major organs resulting in altered mental state (reduced cerebral perfusion), reduced urine output (renal hypoperfusion) and myocardial infarction.

The effects of decompensated shock reduced perfusion of the pulmonary tissues which results in tachypnoea and respiratory distress, tissue anoxia that causes anaerobic glycolysis which results in metabolic lactic acidosis and destruction of liver cells causing reduced clearance of lactate hence acidosis.

The organs responsible for compensatory mechanisms become exhausted due to ischaemia resulting in: -

a) Reduced activity of the medullary vasomotor centre
b) Reduced myocardial activity due to ischaemia, overload and lactic acid accumulation
c) Heart failure
d) Pulmonary hypoperfusion and oedema

e) Reduced renal function causing acute renal failure (ARF) and acute tubular necrosis (ATN)
f) Lungs – respiratory distress syndrome (RDS) and shock lung
g) Gastro-intestinal tract – necrotic changes liberate endotoxins and vasodilating substances, which worsen the state of shock.
h) Liver failure due to reduced metabolic and biotransformation functions.
i) Tissue anoxia causing anaerobic glycolysis resulting in metabolic lactic acidosis.

Clinical features (Signs & symptoms)

1) Reduced blood pressure
2) Tachycardia
3) Tachypnoea
4) Pulse – thready, weak, rapid
5) External features of excessive sympathetic drive
6) Symptoms and signs related to organ failure

2.3. Stage III - Decompensated (Irreversible) shock

This is the final stage of progression of shock where the individual becomes refractory or does not respond to all forms of therapeutic index. **SURVIVAL IS VIRTUALLY IMPOSSIBLE!!!**

The shock is so severe that the compensatory mechanisms, therapy and control aetiologic factors do not lead to recovery. The principal pathology in this state of shock is **tissue anoxia**. Irreversible shock is characterized by widespread organ failure and malfunction.

The occurrences in irreversible shock are: -

- Persistent widespread vasoconstriction of blood vessels affects the liver, spleen, kidney and intestines.
- Anoxia damages the capillary causing vasodilatation and increased vascular permeability. This causes pooling of blood in the peripheral zones.
- Vasodilatation and increased vascular permeability
- Vasodepressor material (VDM) that causes peripheral vasodilatation. It is produced by spleen and skeletal muscle and inactivated in the liver
- Myocardial ischaemia with resultant release of myocardial depressant factor (MDF).
- Cerebral ischaemia
- Failure of the liver to inactivate vasodepressor material (VDM) produced by the spleen and skeletal muscle. VDM causes peripheral vasodilatation.

Features

The main features in this stage include: -
1) Progressive fall in blood pressure
2) Severe metabolic acidosis due to anaerobic glycolysis
3) Respiratory distress
4) Altered function of the brain cells leading to altered consciousness or coma, cardiac and renal function due to ischaemia of the respective cells.

2.4. Advanced Shock

Introduction

If shock persists the widespread arteriolar constriction wears off but the venous constriction is more persistent and capillary pressure rises leading to loss of fluid into the extravascular space and a further fall in blood volume. The capillaries are congested with slowly moving blood and cyanosis may occur. There is hypoglycaemia, metabolic acidosis and reduced heat production.

Changes seen in Blood

1. The viscosity of blood is increased as a result of haemoconcentration due to plasma loss.
2. Release of thromboplastin from hypoxic endothelium and tissue cells leads to thrombosis and promote platelet aggregation causing disseminated intravascular coagulopathy (D.I.C)
3. Neutrophils polymorphs adhere to the injured vascular endothelium
4. Hypoxic injury leading to lysosomal enzymes and proteolytic enzymes.

Changes in Cell Metabolism

Acute hypoxia inhibits respirator and energy utilization systems of the affected cells resulting in pyruvic and lactic acid build up within the cell causing metabolic acidosis.

Catecholamines inhibit insulin release and reduce peripheral glucose uptake resulting in accumulation of glucose in blood (hyperglycaemia). There is more glucose release from the storage form of glycogen under the influence of glucagon as a result of increased gluconeogenesis and triglyceride formation. In some instances, hypoglycaemia ensues due to depletion of hepatic glycogen stores. Increased synthesis of free fatty acids leads to hyperlipidemia. Lack of ATP results in anaerobic metabolism yielding a lot of H+ ions causing acidosis.

Inadequate ATP production results in failure of the sodium pump causing retention of sodium and water within the cell with elimination of K+. This facilitates movement of water into the cell – "sick cell syndrome" further aggravating water and electrolyte imbalance.

3.0 OUTCOME OF SHOCK

1. Recovery – after convalescence
2. Survival – with permanent damage to various organs
3. Death

Factors that favour recover

1. Availability of early treatment of the initiating cause and hypovolaemia
2. Age – youth
3. Good general health

Factors favouring progression of shock

1. Delay in treatment
2. Failure to remove the initiating cause

3. Age – old age
4. Poor general health
5. Pre-existing cardiovascular and lung disease
6. Onset of complications – infection and organ damage

4.0 COMPLICATIONS OF SHOCK (ORGAN FAILURE)

1. Metabolic changes
    a) Carbohydrate metabolism
    b) Protein metabolism
    c) Fat metabolism
    d) Water and electrolyte balance
    e) Metabolic acidosis

2. Morphologic complications in the brain, heart, kidney, adrenals, liver, gastro-intestinal tract and other organs

The most important processes inducing complications are: -

a) Vasodilatation with inadequate tissue and organ perfusion
b) Damage to the capillary endothelial lining
c) Activation of clotting factors

4.1. METABOLIC DISTURBANCES

Shock produces a number of intense metabolic derangements.

Carbohydrate metabolism

In early or initial shock hyperglycaemia occurs because of increased hepatic glycogenolysis and the effects of adrenaline and ACTH hormones that antagonise insulin whereas in decompensated (stages II and III) shock hypoglycaemia occurs due to hepatic glycogen depletion, inhibition of gluconeogenesis and increased consumption of glucose by tissues. Increased anaerobic glycolysis occurs resulting in high blood levels of lactate and pyruvate.

Increased glucagons and catecholamine levels stimulate gluconeogenesis and triglycerine formation. There is increased hepatic mobilization of glucose from glycogen.

Synthesis of free fatty acids is usually increased resulting in hyperglyceridaemia. With reduced availability of oxygen, ATP production depends on anaerobic metabolism where glucose is metabolised to pyruvate, which is then converted to lactate instead of entering the Kreb's cycle. The H+ released accumulates in the circulation causing metabolic acidosis. Reduced availability of ATP results in failure of the sodium pump causing accumulation of salt and water within the cells and increases potassium loss.

Protein metabolism

There is increased intracellular protein catabolism and conversion of amino acids to urea.

Fat metabolism

There is a rise in blood fatty acid levels and increased endogenous fat metabolism.

Water and Electrolyte Disturbances

Due to disturbance in carbohydrate metabolism, there is reduced ATP production with resultant reduction in energy for all cell functions. The sodium pump is affected thus potassium and sodium ions leave the cells with water entering the cells causing swelling of the cells "sickle cell syndrome". There is low sodium level (hyponatraemia). Loss of plasma results in haemoconcentration.

Metabolic acidosis

Following reduced blood supply to the kidney, hypoxia of the kidney results in reduced renal function favouring accumulation of acids such as lactate, pyruvate, phosphate and sulphate. Hypoxia leads to lactic acid production as a result of anaerobic gylcolysis (anaerobic metabolism)

4.2. MORPHOLOGIC COMPLICATIONS

The morphologic changes seen in shock are usually due to tissue hypoxia, which causes generation and necrosis of cells in various tissues and organs. Impaired tissue perfusion, microcirculatory abnormalities and defective oxygen utilization results in multiple organ dysfunction syndrome (MODS).

THE HEART

The heart is highly vulnerable to the effects of hypoxia. There is acute heart failure as a result of:
-

- Hypovolaemia and septicaemia
- Ischaemia
- Pancreas produces a myocardial depressant
- Acidosis depresses myocardial function
- Electrolyte imbalance especially potassium affects the functioning of the heart

Mechanism of Heart Failure

1. Hypoxia due to impaired respiratory function and poor coronary circulation when the blood pressure falls below the critical level.
2. Fall in cardiac output resulting in tissue hypoxia that causes further damage to the heart muscle

THE LUNGS

The lungs have a dual blood supply hence they are generally not affected by ischaemia but by other agents as outlined below.

- There is increased respiratory rate due to cardiac failure and reduced tissue perfusion
- Failure of gas exchange

- "Shock lung"
- Pulmonary oedema, alveolar collapse and intravascular fibrin formation
- Embolism
- Infection

Mechanism of Lung failure

1. Circulatory changes in the lung that occur as a result of failed compensatory mechanisms causing congestion and oedema.
2. Circulatory changes result in damage via enzymes, vasoactive substances in conjunction with augmenting factors such as oxygen supply, drugs and cardiopulmonary failure
   a. Damage alveolar epithelium and capillary endothelium resulting in alveolar oedema and haemorrhage
   b. Alveolar collapse
   c. Formation of hyaline membranes
   d. Fibrosis
   e. Emphysema
   f. Bronchioectasis

THE KIDNEYS

Shock causes renal injury due to ischaemia and eventual necrosis of renal cells. There is damage of renal tubular epithelium leads to acute tubular necrosis (ATN) and acute renal failure (ARF). Urine formation is reduced and production stops when BP < 50 mmHg. ARF eventually may progress to chronic renal failure (CRF)

Mechanism

1. Fall in blood pressure
2. Decreased glomerular filtration rate (GFR)
3. Tubular ischaemia and necrosis
4. Retention of waste products

THE BRAIN

Autoregulatory mechanisms maintain blood flow to the brain in shock but if the blood pressure falls to less than 50 - 60 mmHg, ischaemia ensues causing brain damage. Persistent hypotension and cardiac arrest causes the brain to suffer from serious ischaemic damage with loss of cortical function and coma.

ADRENALS

Adrenals show stress response in shock releasing aldosterone, glucocorticoids and adrenaline. In severe shock adrenal haemorrhages occur.

THE G.I.T

There is mucosal and mural infarction resulting in ulcers (Curling's ulcers) and bleeding.

Mechanism

- Ischaemia, Necrosis, Ulceration, Perforation

LIVER

There is focal necrosis and fatty change of the liver impairing its functions. This is due to anoxia.

5.0 PATHOLOGICAL LESIONS IN SHOCK

1. Kidneys - Acute tubular necrosis (ATN) and Glomerular microthrombosis
2. Lungs
   a. Congestion and oedema
   b. Microthrombosis
   c. Hyaline membrane formation
   d. Atelectasis (collapse of the alveolar)
   e. Interstitial oedema
3. Liver - Centrilobular necrosis and fatty change
4. Heart - Fatty change, Sudendothelial haemorrhage, Myocardial infarction
5. Brain - Anoxia an hypoxic encephalopathy causing confusion, delirium and convulsions
6. Adrenals
   a. Massive haemorrhage
   b. Waterhouse-Fredrichsen syndrome (Shock, meningococcal septicaemia and haemorrhage into adrenals)
7. Pituitary gland - Necrosis following hypovolaemia usually due to post-partum haemorrhage (PPH)- Acute pituitary insufficiency (Sheehan's syndrome) and Chronic insufficiency (Simmond's disease)
8. G.I.T
   a. Acute ulceration of stomach and duodenum usually associated with burns (Curling's ulcers/stress ulcers)
   b. Haemorrhage into the interstitial mucosa.

6.0 INVESTIGATIONS

1. Blood
   a. Full haemogram – Haemoglobin, White cell count, Platelets and Coagulation factors
   b. Blood glucose
   c. Serum creatinine, urea and electrolytes
   d. Liver biochemistry - bilirubin – direct, indirect and total
   e. Blood gases
   f. Blood culture (septicaemic shock)
2. Chest and abdominal radiography (X-ray)
3. Ultrasonography
4. CT scan (computerized tomography)

Lesson 9: Disturbances of Body Fluid Homeostasis (Dehydration and Oedema)

Learning Outcomes

By the end of the unit the learner should be able to: -

1. Describe the fluid regulation mechanisms.
2. Describe the pathogenesis and pathophysiology of oedema
3. Outline water movement patterns in dehydration
4. Outline the clinical features of dehydration
5. Investigation causes of oedema
6. Investigate causes of dehydration

Normal Fluid Balance (Homeostasis)

1.0 INTRODUCTION

Water accounts for 60% of the body weight in males and 50% that of females with the difference in percentage reflecting the differences in the fat content for each gender. In both sexes, water accounts for 75% of the lean body weight (body weight without fat). For the cells of the body to function optimally they should be bathed in **extracellular fluid** with **a relatively constant concentration** of **electrolytes and other solutes**. The concentration of solutes in extracellular fluid (ECF) and osmolarity is determined by the amount of solute divided by the volume of ECF, for instance sodium concentration and osmolarity are regulated by the amount of extracellular water.

2.0 FLUID INTAKE AND OUTPUT

The relative constancy of body fluids is achieved through continuous exchange of fluid and solutes with the environment and within the different body compartments. This implies that fluid intake should balance fluid loss to prevent the fluid volume decreasing or increasing.

Daily Intake of Water

The major sources of water are: -
1. Ingestion of fluids and food – 2250 ml/day
2. Metabolism – 350 ml/day

Daily Loss of Body Water

1. Insensible water loss
2. Sweat
3. Faeces
4. Renal loss (1500 ml/day)

3.0 FLUID COMPARTMENTS

The water is distributed between **intracellular fluid (ICF)** and **extracellular fluid (ECF**) compartments, which are, separated by a cell membrane. The ICF is found inside body cells while ECF is found outside the cells.

1. Extracellular Fluid (ECF)

ECF is divided into: -
1. Plasma
2. Interstitial fluid (fluid outside the circulation)
3. Transcellular water that is found in specialized spaces such as pleura, synovium, intraoccular, cerebral spinal spaces (CSF) and lumen of the gut.

2. Intracellular Fluid Compartment (ICF)

About 28 of the 42 litres of fluid in the body are found inside the 75 trillion cells hence the name intracellular fluid, which constitutes 40% of total body weight.

Blood Volume

Blood contains both **extracellular fluid** (in plasma) and **intracellular** fluid (in the cells e.g. red blood cells). Blood is found in its own compartment that is the circulatory system. Blood volume plays a significant role in controlling cardiovascular dynamics. The average blood volume of adults is 7% of body weight that about 5 litres. 60% of blood is plasma with red blood cells taking the 40%. These percentages vary depending on sex, weight and other factors.

Composition of ECF and ICF

The main cation in ECF is **Na^+** while in the ICF it is **K^{2+} and Mg^{2+}.** The lower intracellular Na and high K levels are maintained by the Na/K pump.

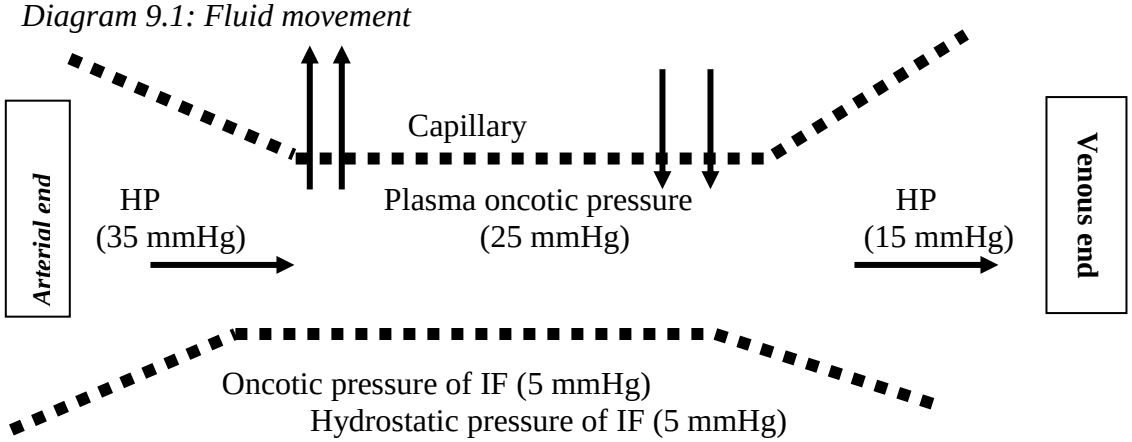
Distribution of Water between ICF and ECF

Movement of water across cell membranes that are freely permeable to water is chiefly by osmotic forces. The cell volume is essential for normal functioning of the cells and it is therefore controlled through regulation of plasma osmolality, which is held within narrow limits.

4.0 FLUID MOVEMENT

Movement of fluid between plasma and interstitial fluid is controlled by the capillary **hydrostatic pressure (HP**) and the **plasma oncotic/osmotic pressure (OP)** and **permeability of capillarie**s to water and solutes. The movement in and out of the interstitial fluid is rapid with 75% of plasma being exchanged every minute.

Diagram 9.1: Fluid movement



Note:

Although albumin concentration in IF is low, 50% of the total albumin is extracellular because the volume of IF is 3-4 times greater than plasma volume.

Osmosis and Osmotic Pressure

Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration. When a solute is added to pure water it reduces the concentration of water in the mixture thus the higher the solute concentration in a solution the lower the water concentration. Normally water diffuses from a region of low solute concentration (high water concentration) to one with high solute concentration (low water concentration). This movement is driven or guided by the osmotic forces or pressure and the rate of diffusion of water is called the rate of osmosis.

5.0 PATHWAYS OF FLUID REGULATION

a) ADH (AVP – Arginine vasopressin)

AVP responds to osmotic tension of the blood plasma. With increased water loss the osmotic tension raises stimulating receptors in the hypothalamus region, which in turn stimulate the posterior pituitary gland increasing secretion of AVP. AVP enhances reabsorption of water at the proximal convoluted tubules and the collecting ducts.

b) Excretion/retention of sodium

Sodium is the principal cation of ECF and its reabsorption/excretion by the kidneys regulates body water. Retention of sodium increases the osmotic tension of plasma facilitating activation of osmoreceptor cells in the anterior hypothalamus prompting the posterior pituitary gland to secrete ADH. The ADH released is transported by blood to the kidneys where it increases water permeability of the distal tubules, cortical collecting tubules and inner medullary collecting ducts causing increased water reabsorption and excretion of a small volume of concentrated urine.

Excess water intake decreases ECF osmolality, less ADH is formed, renal tubules decrease their permeability for water, less water is reabsorbed and a large volume of dilute urine is formed.

Aldosterone produced by the adrenal cortex increases reabsorption of sodium by the renal tubules.

Volume Receptors

Changes in **extracellular fluid (ECFV)** volume are detected as **changes in effective circulating volume (ECF)** by volume receptors in the **carotid sinus, aortic arch** and **afferent glomerular arterioles**. The ECV is the part of ECFV in the vascular space that effectively perfuses the tissues and it varies directly with the ECF but in disease e.g. heart failure ECV may be reduced while the ECF volume in increased. Stimulation of volume receptors causes activation of the **sympathetic system**, **RAA system** and atrial **natriuretic peptide.**

Sodium & Water Retention (Oedema)

1.0. INTRODUCTION

Oedema is abnormal/excess fluid in body tissues such as the interstitial space, cells and cavities. In most instances oedema occurs in the extracellular fluid compartment. Oedema formation can be intracellular or extracellular.

Oedema that occurs in the intracellular tissues results mainly from depression of metabolic systems of the tissues, reduced cell nutrition and inflammation.

Extracellular fluid oedema results from excess accumulation of fluid in the extracellular spaces through abnormal leakage of fluid from plasma to the interstitial spaces at the capillaries and failure of lymphatics to drain the fluid from the interstitial spaces into the blood.

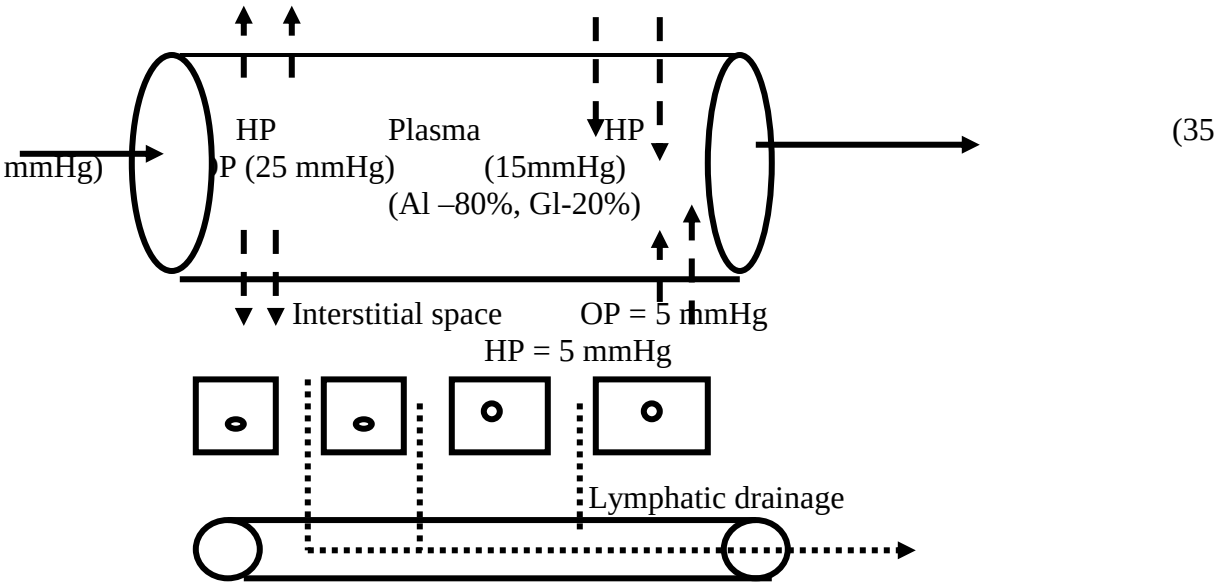
Examination

Firmly pressing on a suspected part for several seconds on clinical examination elicits oedema. The pressure makes the excess fluid between the cells is pushed away leaving an indentation (pitting). The fluid returns to the tissues with withdrawal of the pressure.

Factors Determining partition between Vascular and Interstitial Compartments

Capillaries have an endothelium with physical properties of a semi permeable membrane, which allows passage of fluids across the walls of the blood vessels. This movement is determined by the difference in hydrostatic pressure (HP) and osmotic pressure (OP). At resting conditions, fluid is expelled at the arterial end and re-enters at the venule end. Increased capillary HP or increased OP of the intestinal fluid favours net flow of fluid into the interstitial space from blood.

Diagram 9.2: Fluid Movement



The development of oedema results when the net amount of fluid filtered from the capillaries had exceeded that returned to the circulation (at the venule end or lymphatics).

Causes of the imbalance include: -

1. Increased capillary hydrostatic pressure
2. Decreased capillary oncotic pressure.
3. Fall in interstitial hydrostatic pressure.
4. Increased interstitial oncotic pressure
5. Alteration of the capillary filtration co-efficient
6. Lymphatic insufficiency
7. Defective function of the pre-capillary vasoconstrictor mechanism.

2.0. CLASSIFICATION OF OEDEMA

1. Localized oedema
   a. In an organ
   b. In a limb

2. Generalized oedema
   - ☒ Involves the whole body
   - ☒ Is a hallmark of extra-cellular fluid volume (ECFV) expansion
   - ☒ May be accompanied by formation of free fluid within the serous cavities (ascites, pleural effusion and pericardial effusion)
   - ☒ It is also called Anarsaca/dropsy.

3.0. MECHANISMS OF EXTRACELLULAR OEDEMA FORMATION

The main mechanisms of oedema formation which lead to increased capillary filtration of fluid and protein into the interstitium and increased capillary permeability leading to leakage of proteins and fluid through capillary pores are: - (1) increased capillary hydrostatic pressure, (2) decreased plasma colloid osmotic pressure and (3) increased capillary permeability.

1. Increased capillary pressure (hydrostatic)
   a. Excessive kidney retention of salt and water - Acute or chronic renal failure
   b. High venous pressure (impaired venous return)
      i. Heart failure
      ii. Venous obstruction – thrombosis, pressure
      iii. Failure of venous pumps - paralysis of muscles, immobilized body parts and failure of venous valves
   c. Decreased arteriolar resistance
      i. Excessive body heat
      ii. Insufficient sympathetic nervous system
      iii. Vasodilator drugs

2. Decreased plasma proteins (reduced osmotic pressure)
   a. Loss of proteins in urine (nephrotic syndrome)
   b. Protein losing enteropathy
   c. Loss of protein from denude skin areas – Burns, Wounds
   d. Failure to produce proteins
      i. Liver disease – cirrhosis, hepatoma.
      ii. Serious protein or caloric malnutrition

3. Increased capillary permeability
   a. Immune reactions that release histamine
   b. Toxins
   c. Bacterial infections
   d. Vitamin deficiency e.g. vitamin C
   e. Prolonged ischaemia
   f. Burns

4. Blockage of lymph return
   a. Cancer
   b. Infections (Filariasis – *Wuchereria bacrofti*)
   c. Surgery
   d. Congenital absence or abnormality of lymphatic vessels.

5. Inflammation
   a. Acute inflammation
   b. Chronic inflammation

4.0. LOCALIZED OEDEMA

The oedema is confined to a single part of the body or dingle organ. It results from a local imbalance in forces determining fluid movement between vascular and interstitial compartments.

Causes

1. Pulmonary oedema
2. Cerebral oedema
3. Impaired venous drainage
4. Impaired lymphatic drainage

5. Inflammation
6. Impaired neural control of vessels

4.1. Pulmonary Oedema

Pulmonary oedema is an abnormal increase in amount of interstitial fluid in the lungs. It results from an increase in hydrostatic pressure or a reduction in oncotic pressure within lung capillaries. Initially the fluid accumulates without great change in pressure as the strongly anionic glycoproteins in the loosely structured peri-bronchial connective tissue soak up water as a sponge.

When the capacity of the sponge is exceeded, interstitial swelling extends to alveolar walls and alveoli. The lung lymphatic system provides defence against development of pulmonary oedema as the total lung lymph flow is less than 10 ml/hour but can increase tenfold. In chronic pulmonary venous hypertension there is hypertrophy of the lymphatic, which increases the capacity further.

Engorgement of pulmonary veins and increased interstitial fluid reduces lung compliance and increases the workload needed to move air out of the chest hence the features of dyspnoea/breathlessness. Redistribution of blood between systemic and pulmonary circulation that occurs when moving from upright to horizontal position worsens matters (orthopnoea).

Pathogenesis

1. Excessive pressure changes
   ☒ Changes in capillary hydrostatic pressure and oncotic pressure with normal capillary permeability. The HP is locally increased and OP is reduced.
2. High capillary permeability.

Causes

Pressure Changes

1. Excessive capillary pressure
   ☒ The hydrostatic pressure is locally elevated
   ☒ Any process that directly or indirectly compromises the pumping efficiency of the left side of the heart leads to increased pressure in the left atrium, pulmonary venous and capillary pressure.

   Causes
   a. With venous hypertension - Left ventricular failure (LVF), Mitral Stenosis (MS), Cardiomyopathies, Pulmonary venous thrombosis
   b. With acute pulmonary arterial pressure - Pulmonary emboli, Idiopathic, Drugs

2. Reduced plasma colloid pressure
   a. Nephrotic syndrome
   b. Malnutrition
   c. Malabsorption
   d. Hepatic failure
   e. Overhydration (iatrogenic)

3. Failure of lymph clearance
    a. Malignancy
    b. Mediastinal obstruction
    c. Prolonged inadequate positive pressure ventilation

High capillary permeability

Damage to the pulmonary capillary endothelium leads to increased transudation of fluid into the interstitium and leakage of proteins across the capillary results in formation of oedema with a high protein content. Fibrinogen enters the interstitium and alveoli and coagulates stimulating interstitial fibrosis that impairs lymphatic drainage. High permeability oedema can be caused by mechanical or chemical injury to endothelial capillaries and failure of normal lung defence mechanisms producing damaging inflammatory response.

Causes

1. Hypovolaemic shock
2. Infection in the pulmonary and extra pulmonary (septicaemia)
3. Trauma
4. Embolism (fat, thrombus, amniotic fluid and tumours)
5. Inhalation of gas (smoke, increased oxygen concentration) and liquid (drowning and gastric contents)
6. Haematological - D.I.C, massive blood transfusion.
7. Metabolic - diabetic keto-acidosis (DKA), uraemia, hepatic failure
8. Neurogenic - cerebral oedema, intracranial haemorrhage
9. Drugs/poisons - heroin, aspirin, barbiturates, snake venom
10. Others – pancreatitis, high altitude

What are the signs and symptoms of pulmonary oedema (clinical features)?
What past medical history will be important in a patient with pulmonary oedema?

4.2. Cerebral oedema

Cerebral oedema is increased amount of interstitial fluid in the brain. The symptoms include: - headache, vomiting, drowsiness, visual failure and loss of consciousness.

Causes

1. Cerebral trauma
2. Abscess
3. Haemorrhage
4. Primary and secondary tumours

Mechanism

There is increase in capillary permeability, which is normally reduced in the brain compared to other organs. This occurs at the blood brain barrier (BBB). In the brain there are no lymphatic channels to carry away any excess fluid. “Vasogenic oedema” or “cytotoxic oedema” is the swelling of brain cells due to metabolic injury leading to accumulation of sodium and water

within the cell and a reduction in extracellular fluid (ECF) causing an increase in intracranial pressure (ICP).

The brain cell swelling occurs following ischaemia (focal or general) and complication of water intoxication, hepatic failure, treatment of hypernatraemia and rapid ascend to altitude (mountain sickness).

4.3. Impaired Venous Drainage

Impaired venous drainage occurs due to increased capillary hydrostatic pressure and impaired function of precapillary vasoconstriction mechanism results in increased venous pressure that favours movement of fluid into the tissues. For example leg oedema in deep venous thrombosis (DVT), incompetent venous valves in varicose veins and extrinsic compression of veins by tumours, surgical stockings and plaster of Paris (POP.)

4.4. Impaired Lymphatic Drainage

Impaired lymphatic drainage leads to poor drainage of fluid from the tissues into the blood resulting in retention of fluid.

Causes

1) Congenital hypoplasia (Milroy's disease)
2) Structural damage by neoplastic infiltration and scarring due to trauma and irradiation.
3) Chronic lymphangitis due to *Wuchereria bancrofti* (filariasis), Lymphogranuloma venerium (L.G.V) and recurrent streptococcal infection.

Explain how a patient with Filariasis develops oedema of the lower limb. What is elephantiasis?

4.5. Impaired neural control of vessels

The precapillary vasoconstriction, which requires intact vasomotor innervations, prevents rapid oedema formation when a limb is dependent. These innervations can be disrupted in poliomyelitis. The "muscle pumps" intermittently compress veins and increase venous return of blood to the heart.

4.6. Inflammatory response

Occurs in inflammatory oedema and immunologically mediated reactions such as hypersensitivity reactions – urticaria and angioneurotic oedema.

Explain how oedema is formed in acute inflammation.

5.0. GENERALIZED OEDEMA

Generalized oedema is a consequence of expansion of ECF volume resulting from a period of positive sodium balance with renal excretion of sodium and water failing to keep pace.
Generalised oedema occurs due to intrinsic abnormality of renal function and renal response to inappropriate signs on ECF volume status.

Generalized oedema can be: -

1. Cardiac oedema
2. Renal oedema - Reduced glomerular filtrate (GF), Nephrotic syndrome
3. Hepatic oedema
4. Malnutrition
5. Pregnancy associated oedema - Normal pregnancy, Pregnancy with hypertension

5.1. Renal Oedema

Reduced Glomerular Filtration Rate (GFR)

Profound reduction in GFR leads to maximal rate of sodium excretion by the kidneys being less than ingestion resulting in positive sodium balance. If the glomerulus is affected there is renal tubular sodium reabsorption of which together with reduced GFR leads to virtual cessation of sodium excretion. Sodium retention causes expansion of the ECF and plasma volumes leading to hypertension and/or oedema.

Nephrotic Syndrome

The oedema results from reduction in plasma oncotic pressure due to hypoalbuminaemia following heavy urinary protein loss because of abnormal glomerular capillary. This causes increased filtration and decreased reabsorption on tissue capillaries leading oedema and a contraction of plasma volumes, which precipitates renal salt retention.

Kidneys' role in Na/Water retention

The effector mechanisms by which kidneys retain Na/water in heart failure are: - **Haemodynamic** factors, **Neurogenic** factors and **Hormonal** factors. The three mechanisms are all interacting at any one given time.

Haemodynamic Factors

Heart failure causes a reduction in cardiac output with subsequent reduction in renal blood flow but the glomerular filtration rate (GFR) is relatively persevered by the increased filtration fraction.
In severe cardiac failure the renal blood flow (RBF) and GRF are maintained at rest but with exercise they decrease.

Neurogenic Factors

The sympathetic nervous system may be a mediator of renal vasoconstriction in heart failure.

Hormonal systems

Fall in two main groups of vasoconstriction that promotes Na/water retention (e.g., RAA, AVP, adrenaline and noradrenaline) and vasodilatation that encourages diuresis (e.g. prostaglandins, dopamine and atrial natriuretic peptide (ANF)).

5.2. Malnutrition

This is due to hypoalbuminaemia seen in kwashiorkor. There is gross expansion of the interstitial space associated with reduction in plasma volume.

Describe the pathogenesis and pathophysiology of oedema in a child with malnutrition.

5.3. Hepatic Oedema

Oedema due to hepatic conditions could be due to: -

1) Reduced synthesis of albumin by the liver results in hypoalbuminaemia, which causes reduction in oncotic pressure and plasma volume.
2) Obstruction to hepatic venous outflow e.g. in liver cirrhosis causes reduced urinary sodium excretion encouraging sodium retention.
3) Multiple arterio-venous (A-V) shunts in portal and systemic circulations increase tubular sodium reabsorption.
4) Increased intrahepatic sinusoidal pressure increases sodium retention. Hepatic sinusoids are highly permeable to plasma proteins.
5) Reduced renal blood flow initiates the RAA and aldosterone mechanisms that enhance sodium retention through enhanced sodium reabsorption at the proximal tubules.

5.4. Cardiac Oedema

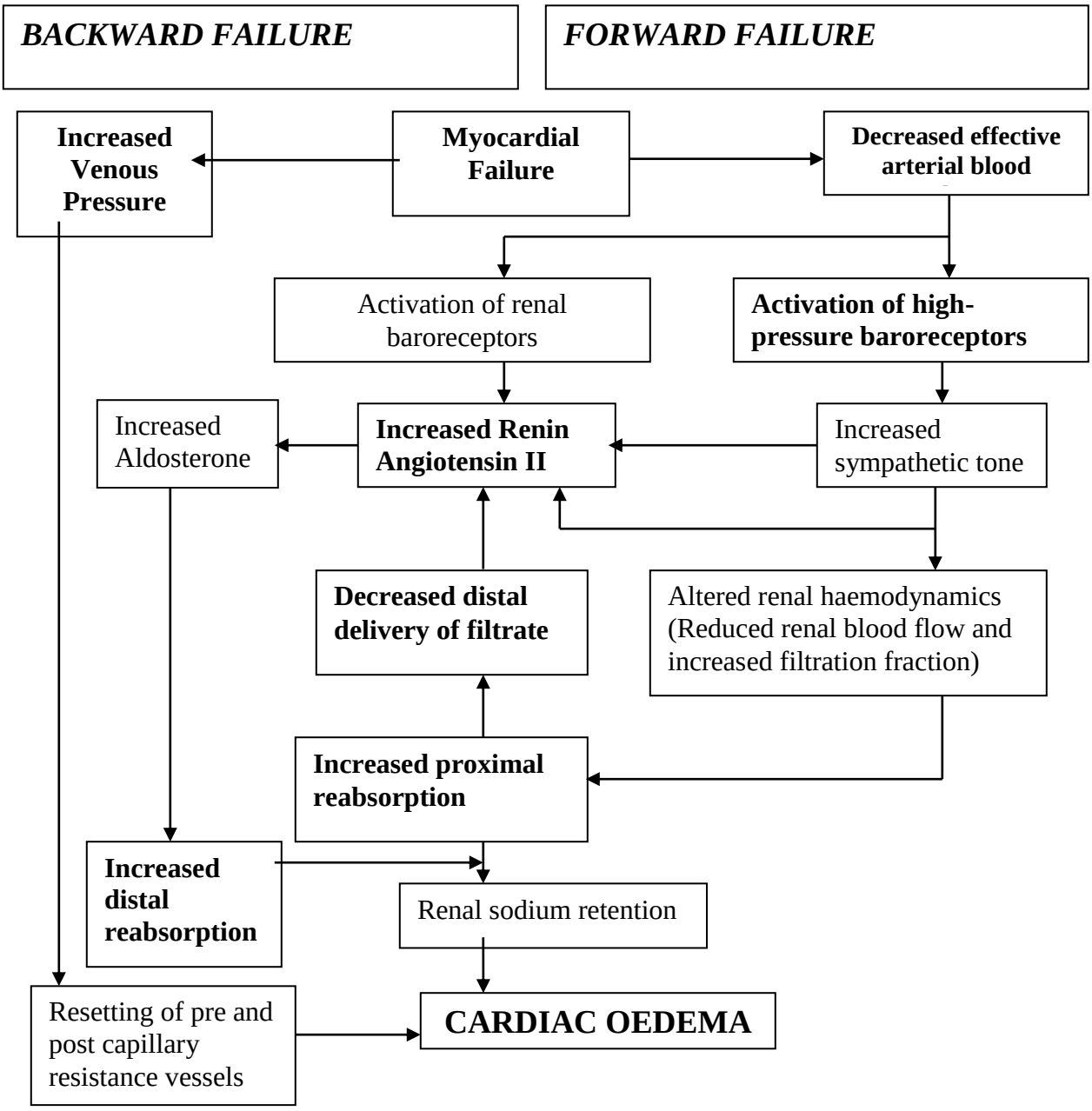
Heart failure is a situation in which the cardiac output is unable to meet the metabolic requirements of the body at rest and during reasonable exercise.

Pathogenesis

The pathogenesis is based on two hypothesis ("forward failure" and "backward failure") and changes in hormonal systems.
"**Forward-Failure**" Mechanism: Inadequate pumping action of the heart leads to disturbance of perfusion of the arterial tree and the receptors perceive this inadequacy of perfusion as an equivalent reduction in blood volume hence they initiate renal responses to conserve sodium and water.

"**Backward-Failure**" Mechanism: Impairment of cardiac function causes an increase in venous pressure leading to increased filtration and decreased reabsorption of fluid by the capillaries causing oedema. Chronic elevation of venous pressure decreases the sensitivity of atrial receptors to stretch allowing congestion and fluid retention.

Diagram 9.4: Pathogenesis of Cardiac Oedema



5.5. Pregnancy induced Oedema

In normal pregnancy, the average weight gain is 12 kg of which 1.25 kg results form expansion of material blood volume and 1.7 kg from accumulation of interstitial fluid at about 30 weeks of gestation to term. Raised levels of plasma rennin and aldosterone suggest that receptor mechanism do not perceive blood volume as raised. Uteroplacental circulation acts as an A-V shunt in distorting perception of plasma volume.

In pregnancy induced hypertension (P.I.H) oedema is present and the plasma volume is reduced compared to normal pregnancy because of abnormal tubular function, reduced uric acid clearance and reduced GFR.

6.0. FLUID IN THE "POTENTIAL" SPACES

6.1. Introduction

This is accumulation of fluid in potential spaces such as the pleural cavity, pericardial cavity, peritoneal cavity and synovial cavities (joint cavity and bursae). These cavities are normally potential spaces with surfaces that almost touch each other with only a very thin layer of fluid between. The little fluid enables the surfaces slide over each other. Fluid accumulating in a potential space is usually referred to an **effusion**. The effusion can be a transudate (protein content – less than 30 gm/L) or exudates (protein content – more than 30 gm/L).

6.2. Pathogenesis

- Normally fluid, electrolytes and proteins are exchanged freely between the capillaries and potential spaces. This means that these spaces are potentially large spaces.
- Lymphatics drain proteins out of the potential spaces and returned to the circulation
- When oedema occurs in the subcutaneous tissues adjacent to the potential space, the fluid also collects in the potential spaces.

6.3. Pleural Effusion

Pleural effusion is accumulation of fluid in the pleural cavity. It can be detected on X-ray when 300 ml or more of fluid is present and clinically when 500 ml or more is present.

Causes

Transudates

1. Heart failure
2. Hypoproteinaemia e.g. nephrotic syndrome
3. Constrictive pericarditis
4. Hypothyroidism
5. Ovarian tumours producing right sided pleural effusion – Meig's syndrome.

Exudates

1. Bacterial pneumonia (common)
2. Carcinoma of the bronchus
3. Pulmonary infarction
4. Tuberculosis
5. Connective tissues disease

Features

a. Reduced chest movement
b. Displacement of the trachea – away from the effusion
c. Reduced chest expansion
d. Decreased vocal fremitus
e. Stony dull percussion note
f. Decreased breath sounds/absent
g. Decreased vocal resonance/absent
h. X-ray – obliteration of costophrenic angle, dense homogenous fluid shadow

6.4. Ascites

Ascites is the accumulation of excessive volume of fluid within the peritoneal cavity. (Askitis is Greek word meaning fluid filled bag). Ascites occurs mainly due to a combination of portal hypertension and hepatocellular failure.

Causes

1. Venous hypertension (congestion) – portal hypertension
   a. Cirrhosis
   b. Congestive cardiac failure (CCF)
   c. Constrictive pericarditis
   d. Hepatic venous outflow obstruction - Budd-Chiarri syndrome, Veno-occlusive disease
   e. Portal vein block
   f. Portal hypertension

2. Hypoalbuminaemia
   a. Liver disease
   b. Nephrotic syndrome
   c. Malnutrition
   d. Protein losing enteropathy

3. Malignant disease
   a. Secondary carcinomas
   b. Lymphomas
   c. Leukaemias

4. Infections
   a. TB peritonitis
   b. Fungal – candida, cryptococcus
   c. Parasitic – strongiloides and entamoeba

5. Miscellaneous
   a. Pancreatitis
   b. Meig's syndrome (ovarian tumour)
   c. Myxoedema
   d. Systemic lupus erythromatosus

Pathogenesis

1. Portal hypertension
   ☒ Portal hypertension exerts a local hydrostatic pressure
   ☒ There is increased hepatic and splanchic production of lymph and transudation into peritoneal cavity

2. Sodium/water retention
   ☒ There is impaired renal functional renal leading to inability to excrete sodium hence the resultant accumulation of sodium.

- ☒ Reduced effective systemic blood volume due to splanchic pooling of blood triggers mechanisms that enhance retention of fluid in the body.
- ☒ Ischaemia activates the RAA system that facilitates retention of fluid in the body.
- ☒ Renal sympathetic system increases proximal convoluted tubules reabsorption of sodium and fluids.
- ☒ Increased plasma norepinephrine
- ☒ Increased ADH (AVP) due to failure of inhibition of vasopressin by prostaglandin E (from the collecting ducts).

3. Hypoalbuminaemia
   - ☒ Reduced oncotic pressure favouring fluid exudation into the cavities.
4. Reduced oncotic pressure
   - ☒ Allows exudation of fluid into the peritoneum across the osmotic gradient established.
5. Distortion and obstruction of hepatic sinusoids
   - ☒ Allows seepage of hepatic lymph into the peritoneal cavity.
6. Renal factors - Patients with ascites fail to excrete water load in the normal way.

Methods of Detection of ascites

1. Ultrasound
2. CAT
3. Diagnostic aspiration
4. Physical examination
   a. Abdominal distension – bulging flanks that are dull to percussion with the umbilical region hyper-resonant (due to floating bowel)
   b. Fluid thrill
   c. Shifting dullness
   d. Positive Puddle sign

Water and Sodium Loss (Dehydration)

Introduction

Fluid in the body is contained in two main compartments – intracellular and extracellular compartments.

Extracellular fluid is found in the **plasma** and **interstitium** and contains mainly **Na^+, Cl^-** and **HCO_3^-** and small portions of K^+, Ca^{2+}, Mg^{2+}, PO_4^- and organic acid ions, proteins (plasma has more proteins than interstitial fluid) and non-electrolytes such as glucose, urea, fat, phospholipids, bilirubin, traces of bile salts and cholesterol. It forms the **internal environment** of the body cells (cells are bathed in the right environment)

Intracellular fluid is found inside the cells and contains large amounts **of K^+ and PO_4^-,** moderate amounts of SO_4^{2-} and $Mg2^+$ and sall amounts of Na^+, Cl^-. It has large amounts of proteins (four times more than that in plasma).

Interstitial fluid contains **low protein** content compared to intravascular (plasma) and intracellular fluid and should remain isotonic with intravascular fluid (IVF) and intracellular

fluid (ICF). It has a **higher electrolyte concentration**, which balances the colloid osmotic pressure of their proteins. Deficiency of sodium and water disturbs this equilibrium in interstitial fluid.

Water Deficiency

Water deficiency causes hypertonicity of extravascular fluid causing water to be withdrawn from the cells resulting in primary dehydration. The resulting loss water leads to a state of deficiency referred to as - **dehydration.**

Diagram 9.5: Movement of Water in Normal equilibrium

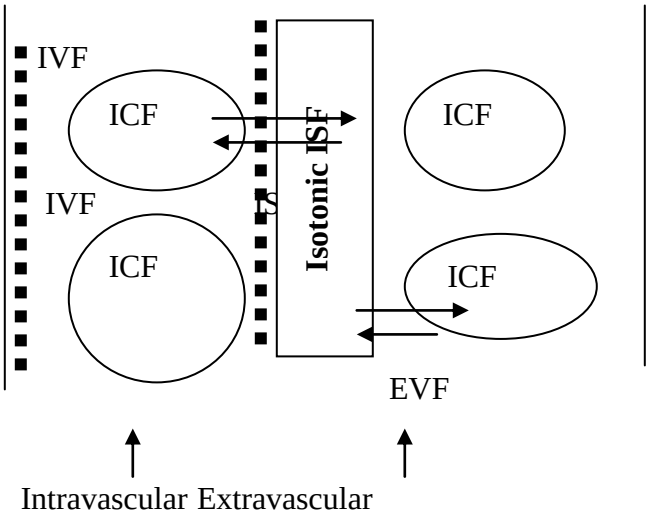
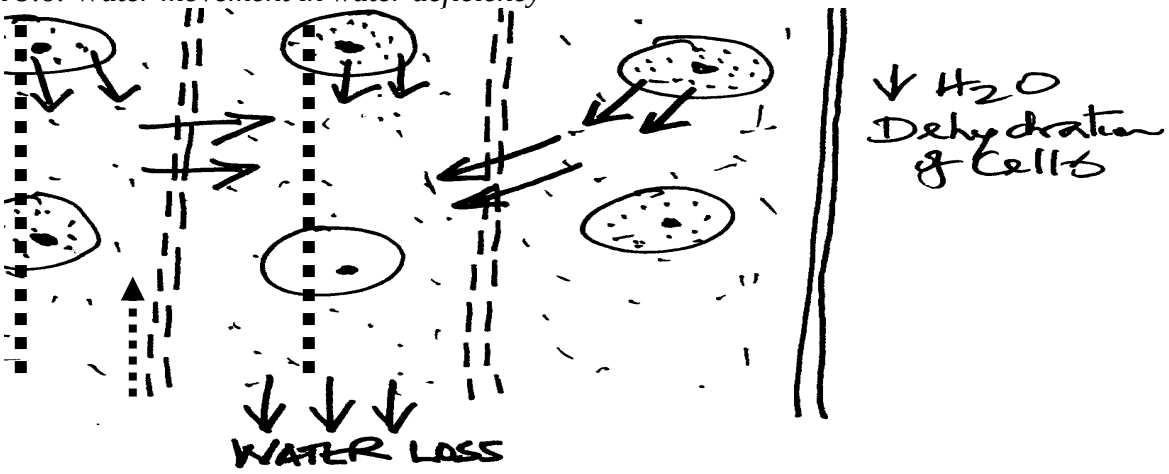


Diagram 9.6: Water movement in water deficiency



If **a hypertonic solution** is added to the **extracellular fluid**, **osmolarity** of the extracellular fluid **increases** causing osmosis of **water from the intracellular compartment to the extracellular compartment**. All the added sodium chloride remains in the extracellular compartment and fluid diffuses from the cells into the extracellular space to achieve osmotic equilibrium. The net effect is **increased extracellular fluid volume, decreased intracellular volume and increased osmolarity of both compartments.**

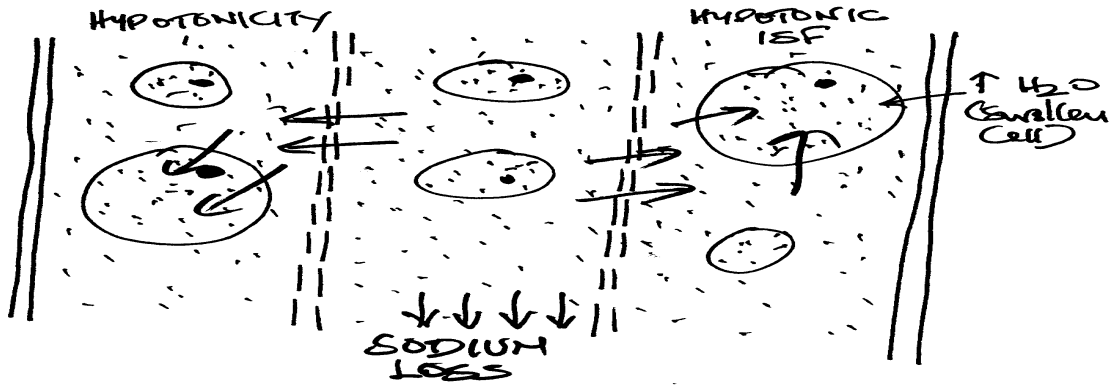
Addition of a hypotonic solution to extracellular fluid decreases osmolarity of ECF and some of the extracellular water diffuses into the cells to achieve an osmotic equilibrium. Both fluid volumes increase more so the extracellular volume.

Salt Depletion

Salt depletion **causes hypotonicity of extracellular fluids** causing water to be drawn into the cells. This effect is minimised by increased renal excretion of water and diffusion of water into the cells from the interstitial fluid therefore maintaining isotonicity of ECF. In salt depletion, ECF are reduced in volume. Administration of glucose and water without salt dilutes ECF and increases diffusion of water into the cells ===**harmful.**

The plasma volume is maintained by withdrawal of intracellular water by active reabsorption of sodium and excretion of potassium under the influence of RAA (reaction of dehydration). In children the body surface area: body weight ration is greater than in adults hence increased loss of fluids causing severe effects. Death results from increased osmotic pressure of the cells.

Diagram 9.7: Water movement in salt depletion



Dehydration

Definition

Dehydration is loss/removal of fluid.

Causes

1. Insufficient intake - Physical weakness, Coma, Pyrexia
2. Fluid Loss
    a. Skin – Burns, Sweating, Exfoliative dermatitis
    b. G.I.T – Diarrhoea, Vomiting,
    c. Endocrine - DKA (diabetic keto-acidosis)

Vomiting is complicated by **alkalosis** due to loss of hydrogen ions while diarrhoea is complicated by **acidosis** due to loss of alkaline secretions of the small intestines. Severe salt loss lowers the osmotic pressure of ECF leading to renal reabsorption of water which facilitates osmotic absorption of water by tissue cells resulting in severe depletion of both ISF and IVF causing circulatory collapse (**shock**).

Vomiting

Vomiting is the forceful ejection of gastric contents through the mouth. It has three phases of nausea, retching and vomiting. Nausea is a feeling of wanting to vomit and is usually associated with autonomic effects e.g. hypersalivation, pallor and sweating. Retching is a strong involuntary effort to vomit.

Causes of Vomiting

1. Any gastrointestinal disease
2. Acute infections
3. Central nervous disease
    a. Raised intracranial pressure e.g. S.O.L (space occupying lesions e.g. brain tumour, brain abscess.
    b. Meningitis
    c. Vestibular disturbances
    d. Migraine
4. Metabolic causes – Uraemia, Diabetes, Gastroparesis, Hypercalcaemia
5. Drugs e.g. opiates, digitalis toxicity, cytotoxics
6. Reflex e.g. severe pain
7. Psychogenesis
8. Pregnancy (hyperemesis gravidarum)
9. Alcohol excess

Diarrhoea

Diarrhoea is passing of increased amounts (> 300 gm per 24 hours) of stools with increased fluidity and frequency.

Causes of Diarrhoea

Acute Diarrhoea

1. Dietary indiscretion
2. Infective e.g. food poisoning (*Staph. aureas, E. coli, Bacillus, Clostridium perfringes, Clostridium boltulinum, Salmonella enteritidis/typhimurium, Compylobacter jejuni and Shigella* spp.) and viral gastroenteritis (rota virus and enteric adenovirus)
3. Traveller's diarrhoea – *Escherichia coli, Giardia intestinalis, Shigella, Entamoeba histolytica, Salmonella and Rota virus*.

Chronic diarrhoea

1. Inflammatory bowel disease
2. Parasitic/fungal infections
3. Malabsorption
4. Gut resection
5. Drugs
6. Colonic neoplasia
7. Endocrine – pancreatic tumours, carcinoma of thyroid, thyrotoxicosis, diabetic neuropathy.
8. Faecal impaction in the elderly

Lesson 10: Electrolyte Imbalance

Learning Outcomes

By the end of the unit the learner should be able to: -

1. Name all the important electrolytes in the body
2. Describe the metabolism and balance of sodium and potassium.
3. Outline causes of deficiency or excesses of sodium and potassium.
4. Describe the effects of excess or deficiency of sodium and potassium.
5. Describe the clinical features associated with excess or deficiency of electrolyte imbalance
6. State the investigations necessary to determine the concentrations of sodium and potassium.

1.0. INTRODUCTION

The kidney maintains the body fluids at a constant composition hence preserving the internal environment by balancing water intake and loss by excreting surplus water. It plays an important function in maintenance of water and electrolytes balance and the blood pH. This is usually achieved during the process of urine formation. The body fluids contain positively charged ions (cations) and negatively charged one (anions) whose composition is different in the intracellular and extracellular fluids.

Body water contains dissolved mineral salts called **electrolytes** that are chemical compounds that ionise in a solution e.g. acids, bases and salts. The body fluids are electrically neutral and the sum of the positively charged ions is balanced by the sum of the negatively charged. Positively charged ions are called **cations** and negatively charged one **anions**. In disease, concentrations of individual ions vary but their electrical neutrality is always maintained.

The kidney excretes ingested inorganic ions, which are surplus to the body requirements (sodium, potassium, magnesium, calcium, chloride etc) hence maintaining electrolyte balance. Clinically, the most important are the sodium ions (Na^+), potassium ions (K^+) and hydrogen ions (H^+).

Table 1: Electrolyte composition

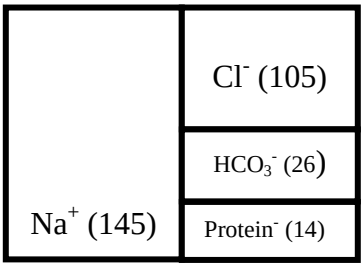
	Plasma (mmol/L)	**Interstitial Fluid (mmol/L)**	**Intracellular Fluid (mmol/L)**
Cations			
Na^+	142	144	10
K^+	4	4	160
Ca^{2+}	2.5	2.5	1.5
Mg^{2+}	1	0.5	13
Anions			
Cl^-	102	117	3
HCO_3^-	27	27	10

PO_4^{2-}	1	1	57
SO_4^{2-}	0.5	0.5	10
Organic acid	3	4	3
Protein	16	0	65

1.1. Extracellular Fluid (ECF)

The principal ions found in ECF are the positively charged sodium ions (Na^+), negatively charged chloride ions (Cl^-) and bicarbonate ions (HCO_3^-). Plasma differs from ECF as it contains plasma proteins, which are negatively charged at a pH of 7.4. Plasma has sodium as the main positively charged ion with Cl^-, HCO_3^- and proteins as its negatively charged ions.

Diagram 10.1: Composition of Extracellular Fluid



The total osmotic concentration = 145+145 (105 + 26 +14) = 290 mmol/L., glucose is 5 mmol/L and urea 5 mmol/L., therefore the total osmotic pressure is 300 mmol/L

1.2. Intracellular Fluid (ICF)

The main positively charges ions found in cells are K and Mg while the negatively charged ions are protein, phosphate and sulphate. The concentration of K^+ in the cells is 150 mmol/L. K and Na have similar chemical properties but they are different substances that are not interchangeable.

2.0. SODIUM

Introduction

Sodium chloride (NaCl) is the principal sodium salt in the body. It is the only inorganic chemical taken in diet as common salt while all the other inorganic requirements are ingested in food. The total amount of sodium in the body is 4000 mmol/L but the normal amount in plasma is 135 – 150 mmol/L.

Sodium balance is maintained by controlling sodium chloride intake and loss. Sodium chloride is gained by ingestion of common salt or through intravenous transfusion of isotonic saline.

The body usually loses sodium in urine and through sweat. Normally sodium chloride intake exceeds the losses through sweat and hence the surplus is excreted in urine. There is a high turnover of NaCl in the kidney with a daily glomerular filtration (GF) of 170 litres of water

containing 0.9 % NaCl leads to filtration of NaCl of about 1500 gm of which 15 gm appear in urine and 1485 gm is reabsorbed each day.

Regulation of Sodium

Maintenance of sodium balance is under the control of hormone aldosterone from the adrenal cortex. Aldosterone increases reabsorption of sodium by the kidney tubules and reduces the sodium content of sweat.

Functions of Sodium

1. Regulation of fluid volume (ECF)
2. Action potential in membrane potentials
3. Muscle contraction/smooth muscle activity
4. Rod function
5. Nerve conduction
6. Olfactory cell stimulation

DISORDERS OF SODIUM CONCENTRATION

Disturbances of sodium concentration are caused by disturbances of water balance.

Hyponatraemia

Hyponatraemia is low sodium levels (below 135 mmol/L). It may be associated with normal extracellular volume and total body sodium content, reduced extracellular volume or increased extracellular volume.

Primary loss of sodium chloride results in hypo-osmotic dehydration, which is associated with decreased ECF volume. This is encountered in conditions such as excessive sweating, diarrhoea, and vomiting and injudicious use of diuretics. Hyponatraemia can be associated with excess water retention that dilutes sodium in ECF a situation termed hypo-osmotic overhydration e.g. when there is excessive secretion of vasopresin.

Causes

Decreased extracellular volume

The following conditions will cause reduced sodium with a reduced ECF.

1. Inadequate intake
2. Abnormal losses
    a. Skin – Sweating, Fever, Burns
    b. Kidneys - Osmotic diuresis e.g. in severe uraemia, hyperglycaemia, Diuretics and Adrenal insufficiency (reduced aldosterone)
    c. Intestines – Vomiting, Diarrhoea, Haemorrhage , Fistula,

Normal extracellular volume

The following conditions will cause reduced sodium with a normal ECF.

1. Abnormal ADH release - Decreased ACTH (Addison's disease), Hypothyroidism
2. Inappropropriate antidiuretic hormone – Stress, Surgery, Nausea
3. Major psychiatric illness e.g. antidepressant therapy
4. Increased sensitivity to ADH – chlorpropamide, tolbutamide
5. ADH-like substances e.g. oxytocin
6. Substances stimulating osmotic ADH release – glucose, alcohol, mannitol and sickle cell

Increased Extracellular volume

The following conditions will cause reduced sodium with an increased ECF.

1. Excessive water retention
   a. Inappropriate ADH secretion
   b. Congestive cardiac failure
   c. Nephrotic syndrome
   d. Oliguric renal failure

Clinical Features

Excessive ingestion of water dilutes the body fluid causing hyponatraemia. Any increase in water reduces the concentration of Na and K. Excessive water intake causes water intoxication resulting from movement of water into the brain cells causing neurological features. The features occur at sodium levels of 120 mmol/L but are more evident at 110 mmol/L.

Features include

1) Cell oedema
2) Headache
3) Vomiting
4) Painful cramps (Stoker's cramp)
5) Cerebral overhydration may cause headache, confusion, fits and even death.

Hypernatraemia

Hypernatraemia is increased sodium level above 150 mmol/L. It is rare and indicates a water deficit.

Causes

1. Impaired thirst
   a. Failure to drink e.g. unconscious patients, confused patients, infants, damage to thirst centre
   b. Essential hypernatraemia
2. Reduced loss
   a. Renal e.g. diabetes insipidus, acute renal failure, secondary aldosteronism, Conn's syndromes, Cushing's syndrome.
   b. Non-renal e.g. sweating
3. Insensitivity to ADH e.g. lithium, tetracyclines
4. Excessive intake
   a. Oral – see water, salt tablets

b. Parenteral – hypotonic sodium containing fluids (iotrogenic)
5. Solute diuretics - Osmotic diuresis in diabetic keto acidosis (DKA), non-ketotic hyper-osmolar diabetic coma and mannitol administration.
6. Combined causes e.g. coma and hypertonic naso-gastric tube feeding.

Effects/Clinical Features

Hypernatraemia is associated with insufficient water to match the sodium in the body. Features include: -

1) Thirst
2) Dryness of mucous membranes
3) Fever
4) Nervous irritability
5) Withered skin
6) Circulatory shock
7) Decreased urine volume.

3.0. POTASSIUM

Introduction

Potassium is the main positively charged ion in cells (about 150 mmol/L). The amount of potassium in plasma is small (3.3 – 5.0 mmol/L) representing the potassium in transit from the digestive system to the cells where it is stored. Potassium levels in plasma are closely maintained within a narrow range. The usual dietary intake of potassium is 80 – 150 mmol daily upon fruit and vegetable intake while the total potassium content in the body is 3500 mmol/L. potassium is actively absorbed through the G.I.T mucosa. 80% of the intake is excreted in urine and the reminder in stool.

External balance of potassium depends on intake (dietary) and renal excretion, which is regulated by aldosterone and rate of delivery of sodium to the distal tubules (passive component). In very severe diarrhoea there is increased loss of potassium in stool.

Serum potassium levels are controlled by uptake of K^+ into cells, renal excretion and extrarenal losses (e.g. gastrointestinal). Uptake of potassium into cells which is governed by the Na+/K^+-ATPase in the cell membrane and H^+ concentration which is usually stimulated by insulin, β-adrenergic stimulation and theophylines and decreased by α-adrenergic stimulation, acidosis (K+ is exchanged for H+ across the cell) and cell damage or death (results in massive K+ release).

Internal balance of potassium depends on the action of active and passive exchange between intracellular and intracellular compartments. The cell membrane Na^+/K^+-ATPase pump actively transfers K^+ into cells while Na^+ is pumped out in an exercise stimulated by insulin. The exchange of ions takes out three Na^+ from the cells replacing with two K^+ ions from the ECF hence establishing an electrochemical gradient across the cell membrane. The passive component rotates on the pH of the extracellular fluid because acidosis enhances cellular potassium loss while alkalosis promotes/enhances cellular potassium uptake.

Cellular uptake of potassium is enhanced by insulin, adrenaline and aldosterone and influenced by blood [H^+] and plasma toxicity.

Functions of Potassium

1. Cardiac muscle function
2. Smooth muscle function
3. Postsynaptic function
4. Control of blood flow (vasodilator theory)
5. Bone salts
6. Membrane potential
7. Nerve conduction.

Hypokalaemia

Hypokalaemia is reduced concentration of potassium – below 3.3 mmol/L.

Causes

1. Excessive renal loss
   a. Diuresis – diuretics e.g. "loop" diuretics and osmotic diuresis e.g. in diabetes
   b. Metabolic alkalosis (what are the causes of metabolic alkalosis)
   c. Mineralocorticoids excess - (secondary hyperaldosteronism, Conn's syndrome [primary hyperaldosteronism], Cushing's syndrome and steroid therapy).
   d. Acute leukaemia
   e. Drugs e.g. antibiotics – carbenicillin, gentamycin, amphoteric B.
2. Renal disease
   a. Renal tubular acidosis
   b. Renal damage by acute leukaemia
   c. Cytotoxic treatment
   d. Nephrotoxicity – aminoglycosides, amphotericin

3. Increased aldosterone secretion- liver failure, heart failure, nephrotic syndrome, cushing's syndrome, conn's syndrome, ACTH producing tumours
4. G.I.T loss – Vomiting, Diarrhoea, Purgative abuse, Stomal fluid loss, Ileostomy, Fistulae, Ilues/intestinal obstruction, Potassium secreting villous adenomas
5. Shifts between extracellular and intracellular spaces - acute alkalosis, insulin therapy, barium ingestion, vitamin B_{12} therapy and thyrotoxicosis
6. Inadequate intake - Poor diet, Reduced intake

Effects

The effects are seen when potassium level is less than 2.0 mmol/L.

1) Muscular weakness
2) Paralysis (severe cases)
3) Respiratory failure
4) Cardiac arrthymias
5) Abnormalities of electrocardiograph (ECG)

6) Fatigue
7) Polyuria
8) Gastric distension
9) Patient sensitive to digitalis (increases the binding of digoxin to cardiac cells potentiating its action and decreasing its clearance)

Hyperkalaemia

Hyperkalaemia is raised potassium level above 5.0 mmol/L. A level of 7.0 mmol/L is a medical emergency presenting with ECG changes as it causes hyperpolarization of cell membranes leading to decreased cardiac excitability, hypotension, bradycardia and eventual asystole.

Renal potassium excretion is determined by the sum of three renal processes of rate of potassium filtration (GFR X concentration of K), rate of K reabsorption by the tubules and rate of K excretion by tubules. Secreting mechanism for K is shared with that of H ions from surplus acids hence an increase in K^+ and H^+ causes hyperkalaemic metabolic acidosis.

Decreased K cause leads to little K in glomerular filtrate and excretion of acids – hypokalaemic metabolic acidosis.

Causes

1. Excessive intake
   a. Fruit juices
   b. Therapeutic preparations

2. Reduced renal loss
   a. Reduced glomerular filtration rate (GFR) - Acute renal failure, Chronic renal failure
   b. Reduced tubular secretion - Addison's disease, Potassium sparing diuretics – spironolactone, amiloride, ACE inhibitors , NSAIDS, Heparin treatment , Acidosis

3. Shifts between extracellular and intracellular spaces (Increased release from cells)
   a. Acidosis
   b. Cell damage/destruction – haemolysis, trauma/soft tissue damage, burns and tumour cell necrosis
   c. Digoxin overdose
   d. Diabetic hyperkalaemia (rapid)

4. Increased load - Potassium chloride – iatrogenic, salt substitutes, Potassium citrate and Transfusion of stored blood

Effects

1) Lower cell membrane potential
2) Decreased cardiac excitability
3) Cardiac arrest
4) Metabolic acidosis associated with Kussmal breathing
5) Muscle weakness

Note: giving of glucose and insulin leads to transfer of potassium.

3.1. Diuretics

1) Mersalyl – acts at the proximal convulated tubules (PCT)
2) Benzothiadiazine (thiazibne) diuretics e.g. chlorothiazide, hydrochlothiazide, bendrofluazide, hydrofuazide, act at the PCT.
3) Frusemide (lasix) – very powerful
4) Spironolactone – antagonizes aldosterone reducing sodium reabsorption at the distal convulated tubules (DCT).

CALCIUM (Ca)

Introduction

The total body calcium depends on the amount absorbed from dietary intake and that lost from the body. 25 mmol/L (1gm) is ingested per day of which 6-12 mmol/L (0.25 – 0.50 gm) is absorbed. The active metabolite of vitamin D, 1, 25 dehydroxycholecalciferol is required for adequate absorption.

Calcium homeostasis is regulated by the effects of the parathyroid hormone and $1,25(OH)_2$-D_3 on intestinal absorption, renal tubular reabsorption and bone resorption. Calcium sensing receptors present in the parathyroid glands, kidney and brain respond to changes in extracellular calcium concentrations.

Calcium is lost in faeces and urine. Calcium may form insoluble poorly absorbed complexes with phosphate a technique used therapeutically reduce calcium absorption and excretion. Excess fatty acids in the intestinal lumen lead to calcium malabsoprtion. The parathyroid hormone and vitamin D increases renal calcium reabsorption

Plasma Calcium

The mean plasma concentration is 2.50 mmol/L (10 mg/dL) – (2.12 – 2.62 mmol/L) i.e. 8.5 – 10.5 mg/dL. It is present in plasma in two forms. That bound to plasma proteins, mainly albumin which accounts for less than 50% of the calcium in a physiologically inactive form and the free-ionised calcium (Ca^{2+}) that takes the majority and it is the physiologically active form.

Changes in H^+ affect the binding sites on plasma proteins because it competes with Ca^{2+} for the binding sites but the total plasma Ca is not altered with H^+ changes. In alkalosis tetany occurs while in acidosis the proportion of plasma Ca in free-ionised form is increased, Ca solubility is increased and hence an increase in release of Ca from the bones to the extracellular fluid increasing renal loss and eventually osteomalacia.

Control of Plasma Ca

Bone is the reservoir from which both the parathyroid hormone and calcitonin (from the thyroid gland) control free-ionised calcium concentration. The parathyroid hormone increases circulating levels of free-ionised calcium, calcitonin decreases osteoclastic activity and slows calcium

release form the bone and 1,25-dihydrocholecalciferol increases calcium absorption from the intestines and arguments parathyroid hormone activity at physiological concentrations.

Regulation of Calcium Homeostasis

Regulation of calcium homeostasis depends on vitamin D metabolism, parathyroid hormone (PTH), calcitonin and thyroxine hormone

Vitamin D Metabolism

Vitamin D is produced in the skin as cholecalciferol (vitamin D_3) by sunlight photoactivation of 7-dehydrocholesterol. The vitamin D metabolites are transported in circulation bound to vitamin D-binding protein to the liver where cholecalciferol is converted to 25 hydroxycholecalciferol (25-OH-D_3). A renal tubule enzyme 1□hydroxylase converts (25-OH-D_3) to 1,25 dihydroxycholecalciferol (1,25-$(OH)_2$-D_3 - a highly biological active metabolite) and a less active metabolite 24,25-$(OH)_2$-D_3). 1,25-$(OH)_2$-D_3 increases gut calcium absorption, increased bone absorption and increased bone resorption.

Parathyroid hormone (PTH)

Parathyroid hormone is an amino acid hormone secreted by cells of the parathyroid glands. PTH levels rise when serum ionised calcium falls. The calcium levels are detected by calcium-sensing receptors on plasma membrane of parathyroid cells.

The action of PTH serves to increase plasma calcium by: -

- ☒ Increased osteoclastic resorption of bone (a rapid response)
- ☒ Increased intestinal absorption of calcium (a slow reaction)
- ☒ Increased synthesis of 1,25-$(OH)_2$-D_3
- ☒ Increased renal tubular reabsorption of calcium
- ☒ Increased excretion of phosphate

Calcitonin

Plasma levels of calcitonin rise with increasing serum calcium. Calcitonin inhibits osteoclastic bone resorption of calcium and increased renal excretion of calcium and phosphate.

Thyroid hormone

Excess thyoxine (T4) and triiodothyroxine (T3) cause increased bone turnover with hypercalcaemia while hypothyroidism leads to growth delay.

3.2. Hypercalcaemia

Increased plasma levels of calcium.

Causes

1) Increased parathyroid hormone

- Primary hyperparathyroidism e.g. from adenomas, cancer, pheochromoctoma
- Tertiary hyperparathyroidism – e.g. sustained positive feed back by low plasma free-ionised calcium
- Increased parathyroid hormone-related protein – production of the parathyroid-like hormone by a non-parathyroid tissue.

2) Excess activation of vitamin D - Iatrogenic (excess administration), Tuberculosis, Lymphoma, Sarcoidosis
3) Excess calcium intake - "Milk alkaline syndrome"
4) Malignant disease - Secondary deposits in bone, Products of osteoclastic factors e.g. tumours, Myeloma
5) Endocrine disorders – Thyrotoxicosis, Addison's disease
6) Drugs - Thiazide diuretics, Vitamin D analogues, Vitamin A, Lithium administration
7) Miscellaneous - Long term immobility

Effects

☒ Renal damage
- Polyuria – due to impaired concentrating ability of the renal tubules as a result of calcification of tubules reducing response of tubules to ADH.
- Hypokalaemia – calcium inhibits K reabsorption from the renal tubules
- Renal calculi – precipitation of calcium salts in urine
- Haematuria
- Hypertension

☒ Neuromuscular excitability
- Increased free-ionised calcium depresses voluntary and involuntary movement in muscles leading to constipation, abdominal pain and hypotonia.

☒ Central nervous system
- Depresses CNS
- Causes anorexia, nausea and vomiting

☒ Stomach
- Stimulates secretion gastrin that forms gastric acid causing peptic ulceration.

☒ Blood pressure
- Causes hypertension

☒ Heart
- Causes shortening of Q-T complex and broadening of the T waves on the electrocardiogram (ECG)
- Cardiac arrest and ventricular fibrillations if the concentration is over 3.75 mmol/L (15 mg/dL).

Clinical Features

1. Tiredness
2. Malaise
3. Depression
4. Nausea/vomiting
5. Dehydration

6. Polyuria
7. Altered consciousness

Investigations

1. Biochemistry - Fasting serum calcium and phosphate, renal function tests, Serum TSH and T3.
2. Imaging - Abdominal X-ray, Ultrasound, CT scan, Magnetic resonance imaging (MRI)

3.3. Hypocalcaemia

Hypocalcaemia is reduced plasma calcium levels.

Causes

1) Inadequate intake or absorption of calcium
2) Hypoparathroidism
3) Chronic renal failure
4) Pancreatitis

Effects

1) Rickets
2) Osteomalacia
3) Tetany
4) Bone pains
5) Pseoudoporosis

Clinical Features

1. Neuromsucular irritability
2. Neuropsychiatric manifestations
3. Cramps
4. Anxiety
5. Laryngeal stridor
6. Dystonia
7. Chvostek's sign (gentle tapping over the facial nerve causes twitching of facial muscles)
8. Trousseau's sign (inflation of sphygmomanometer for 3 minutes induces titanic spasms of fingers and wrist)
9. Papilloedema
10. ECG changes – prolonged QT interval

4.0. MAGNESIUM

Introduction

Plasma magnesium levels are maintained within a range of 0.7 – 1.1 mmol/L with the balance being the function of intake and excretion of magnesium. The major site of Mg transport is the thick ascending limb of the loop of Henle where 50 – 70% of filtered Mg load is reabsorbed. Loop magnesium reasorption varies with plasma magnesium concentration, which is the main physiological regulator of urinary magnesium excretion.

Hypomagnesaemia inhibits loop transport while hypomagnesaemia stimulates Mg transport. Hypercalcaemia inhibits loop transport. Sodium chloride reabsorption can also influence loop magnesium transport.

Hypermagnesaemia

Increased plasma magnesium level
Causes

1. Impaired renal excretion - Chronic renal failure (CRF), Acute renal failure (ARF)
2. Increased Mg intake - Purgatives e.g. magnesium sulphate, Antacids e.g. magnesium triscilicate
3. Haemodialysis with high [Mg^{2+}] dialysate
4. Adrenal insufficiency

Clinical Features

Signs and symptoms relate to neurological and cardiovascular depression. The symptoms develop when plasma levels exceed 2 mmol/L.

1) Weakness
2) Hyporeflexia
3) Respiratory paralysis
4) Cardiac conduction effects
5) Narcosis

4.1. Hypomagnesaemia

Reduced plasma magnesium levels

Causes
1. Decreased Mg absorption
    a. Severe malabsorption
    b. Malnutrition
    c. Alcohol excess

2. Increased renal excretion
    a. Drugs – loop diuretics, thiazide diuretics, digoxin
    b. Diabetic keto acidosis (DKA)
    c. Hyperaldosteronism
    d. 1,25 OH-vitamin D deficiency
    e. Drug toxicity – amphoteric, cyclosporin, aminoglycosides

3. Gut losses
    a. Prolonged nasogastric suction
    b. Excessive purgation
    c. Gastrointestinal and biliary fistulae
    d. Severe diarrhoea

4. Miscellaneous – acute pancreatitis

Clinical Features

1) Irritability
2) Tremors
3) Ataxia
4) Carpopedal spasm
5) Hyperreflexia
6) Hallucination states
7) Confusional states
8) Epileptiform convulsions
9) ECG changes – prolonged QT interval, flattened T waves and short ST segment.

5.0. PHOSPHATE

Phosphate is an essential part of most biochemical systems. 80% of all body phosphorous is within the bone and plasma. Plasma phosphate level is 0.08 – 1.40mmol/L. Phosphate reabsorption from the kidney is influenced by parathyroid hormone whereby hyperparathyroidism leads to low plasma levels of phosphate. Regulation of plasma phosphate is closely related to calcium.

5.1. Hypophosphataemia

Causes

1. Redistribution of phosphate
    a. Respiratory alkalosis
    b. Treatment of diabetic keto acidosis (DKA)
    c. After parathyroidectomy
2. Renal losses
    a. Diuresis
    b. Renal tubular defects
    c. Hyperparathyroidism
3. Reduced intake/absorption
    a. Dietary
    b. Malabsorption
    c. Vomiting
    d. Gut phosphate binders e.g. aluminium hydroxide
    e. Vitamin D deficiency or resistance
    f. Alcohol withdrawal

Clinical Features

1) Muscle weakness - Diaphragm weakness, Decreased contractility, Skeletal muscle
2) A left shift in the oxygenhaeomglogin
3) Confusion
4) Halluscinations
5) Convulsions

5.2. Hyperphosphataemia

Causes

1) Chronic renal failure
2) Phosphate containing enemas
3) Tumour lysis.

IV FLUIDS

Depletion of fluids and electrolytes in the body is usually corrected by giving fluids either orally (oral rehydration) or by intravenous route (IV infusions). All fluids given intravenously must be sterile and isotonic with blood.

Commonly used fluids

1. Normal saline
2. Dextrose
3. Ringer's solution
4. Ringer's lactate
5. Darrow's solution
6. Half strength Darrow's (HSD) solution
7. Hartman's solution
8. ORS
9. Rasomol

◇ Find out the composition of these IV fluids.
◇ When and why are they used?