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A Detail Review On Need Of Anticoagulants In The Treatment Of Cardiovascular Illness.

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Abstract:

Blood is expressed as specialized connective tissue that contains liquid intercellular substances called plasma and formed components such as the blood cells, the white blood cells and the platelets which are suspended in plasma. Although blood serves a major function to deliver oxygen and nutrients to the whole body and eliminate waste from body cells and it performs several other functions. This article gives a general overview of blood and its components. Also, it includes detailed information on platelets and their roles. The role of blood includes defense against disease and distribution of heat, as well as maintenance of homeostasis.

Although, this article provides comprehensive detail on the anatomy, physiology of blood coagulation and anticoagulation process. For all its similarities in origin, composition, and functions, blood is as unique from one person to another as are skin, bone, and hair. Health care professionals routinely examine and analyze its differences through various blood tests when trying to determine the cause of different diseases. Blood carries various components which help to regulate several life processes and affords protection against disease. As each blood component has a distinct purpose, this overview focusses on how component separation has improved the usage of a single whole blood unit, platelet production, and disease condition.

Keywords:

Blood, RBC, WBC, Platelets, Plasma.

Introduction:

Blood is an essential body fluid. It is key for life; without blood the cell and tissue will die. Blood feels sticky and, as the saying goes, is thicker than water (viscous). The body temperature is approximately one degree lower than the blood temperature, which is 38 degrees Celsius. The volume of blood a person has in their body is mostly dependent on size, weight and gender. The average person's blood volume is around 4.5 to 5.5 liters of blood. Blood accounts for about 4.5 to 5.5 kg. An infant weighing about 2.3 to 3.6 kg has about 0.2 liters of blood in their body. When a child reaches the age of five or six, their blood volume is roughly equal to an adult. (1)

Blood is a liquid organ that can save lives. A variety of substances, including cellular components, colloids, and crystalloids, make up whole blood. Centrifugal force can be used to separate distinct blood components since they differ in size, relative density, and sedimentation rate. Of all the components of blood, leucocytes (Buffy Coat [BC]), packed red blood cells (PRBCs), platelets, and plasma have the highest specific gravities. For one blood unit to be used properly and appropriately, component therapy must be universally modified. Each component's ability to work effectively depends on how it is processed and stored. (2) Blood is only fluid connective tissue that nourishes all the body's cells while pumping blood through the heart, arteries, and veins. Blood contains formed elements such as red blood cells, white blood cells, platelets and a fluid component called plasma. (1,2) A clear, straw-colored, watery fluid called plasma, in which various blood cell types are suspended, makes up blood. The usual composition is plasma. 55% of the blood volume and 45% of the cell fraction. A whole blood sample separates into its plasma fraction and its cellular fraction after being carefully centrifuged and combined with an anticoagulant to avoid clotting. (3) Among the components of blood, platelets are essential. It is crucial for preserving appropriate hemostasis and forming blood clots. Vascular damage causes hyperactive platelet activation under pathologic conditions like atherosclerosis, which can lead to myocardial infarction, stroke, and occlusive thrombus development. Outlining our present knowledge of blood anatomy, physiology, and pathology is the main goal of this review. Some features regarding the platelets and their disorders. (4)

Anatomy and Physiology of Blood:

Blood is the fluid connective tissue it moves constantly around the body, propelled by the pumping action of heart and constant communication between tissues distant from each other. (3)

It transports: - dissolved gases including oxygen, nutrients, hormones, heat, antibodies and cells of the immune system, plasma proteins, including clotting factors, drugs, and wastes. Blood is made up of transparent, straw-colored watery substances called plasma, which contain different types of cells.

Normal Blood volume is Composed of 45% cell fraction and 55% of plasma. A whole blood sample, mixed with an anticoagulant to prevent clotting and gently centrifuged, separates into its plasma fraction and its cellular fraction. The cells are heavier than plasma and sink to the bottom of the sample. Gentle shaking or stirring of the sample will respond in the plasma cell, reconstituting the whole blood. (3,5)

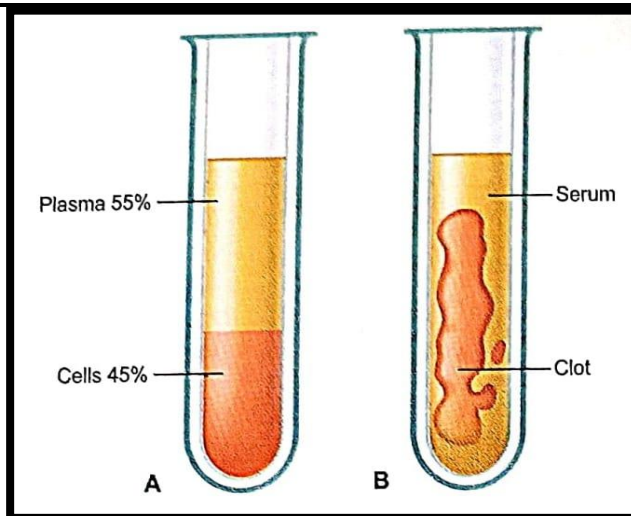


Fig 1. Whole blood: (A) The proportion of blood cells and plasma in anticoagulated when blood separated by gravity (B) A blood clot in serum. (1)

Physical characterization of blood:

Blood makes up about 7% of body weight (about 5.6 liters in the 70kg man). This proportion is less in women and considerably greater in children gradually increase until adult level is reached. The total blood volume in adults about 80mL/kg body weight in males and 70 mL / kg in females (3). The gender difference in the volume due to difference in body size, several hormones, regulated by negative feedback, ensure that body volume and osmotic pressure remain constant. The temperature of blood is 38°C (100.4°C), about 1 degree Celsius higher than oral or rectal temperature. (5) Blood maintains the core body temperature by distributing heat produced by metabolically active organs such as working skeletal muscles and the liver around the body. And it has a slightly alkaline pH ranging from 7.35 to 7.45(Average=7.4). Blood's colour changes according to its oxygen content. It turns bright red when oxygen is present. It is dark red when oxygen is unsaturated. Blood constitutes 20% extracellular fluids. Total blood volume and concentration of blood constituents, for example glucose and electrolytes are kept within narrow limits like homeostatic mechanism. (3,5)

Functions of blood:

The three major functions of blood: -

1. **Transportation:** - Blood carries carbon dioxide out of body cells and oxygen from the lungs to the body's cells for expiration. Hormones from endocrine glands are transported to other body cells by it, as are nutrients from the gastrointestinal tract. Blood also transports heat and waste products to various organs for elimination from the body. (5)
2. **Regulation:** - Blood circulation helps to maintain homeostasis of all body fluids. Blood uses buffers to regulate pH. It helps in adjust body temperature through heat absorbance and coolant properties of water in the plasma and its variable rate of flow through the skin which allow extra heat to escape from the blood to surrounding air. And it also regulates osmotic pressure and influences the water content of cell.
3. **Protection:** - After an injury, the ability of blood to clot (become gel-like) guards against excessive bleeding from the cardiovascular system. Additionally, its white blood cells continue phago-cytosis to prevent sickness. Several types of blood proteins, including antibodies, interferons and complements, help protect against disease in a variety of ways. (3,5)

Components of blood:

The whole blood has 2 components-

1. Blood plasma (A Watery liquid, Extra cellular matrix that contains dissolved substance).
2. Formed elements (which are cell and cell fragment).

If sample blood centrifugation in small test tube the cell sick to the bottom of test tube, while plasma forms layer on the top, the blood is about 45% formed element and 55% blood plasma.

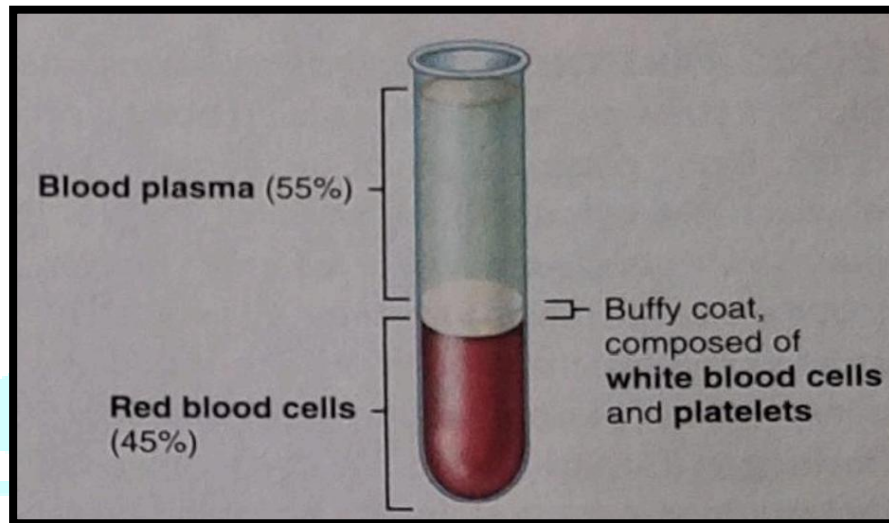


Fig 2. Appearance if centrifuged blood. (5)

On average, over 99 percent of the elements that are generated are red blood cells (RBCs), which are named for their red colour. Pale, colorless white blood cells (WBCs) and platelets occupy less than 1% of the formed elements. Because they are less dense than red blood cells but denser than blood plasma, they form a very thin buffy coat layer between the packed RBCs and plasma in centri- fudged blood. As the figure shows the composition of blood plasma and the number of various types of formed elements in blood. (5)

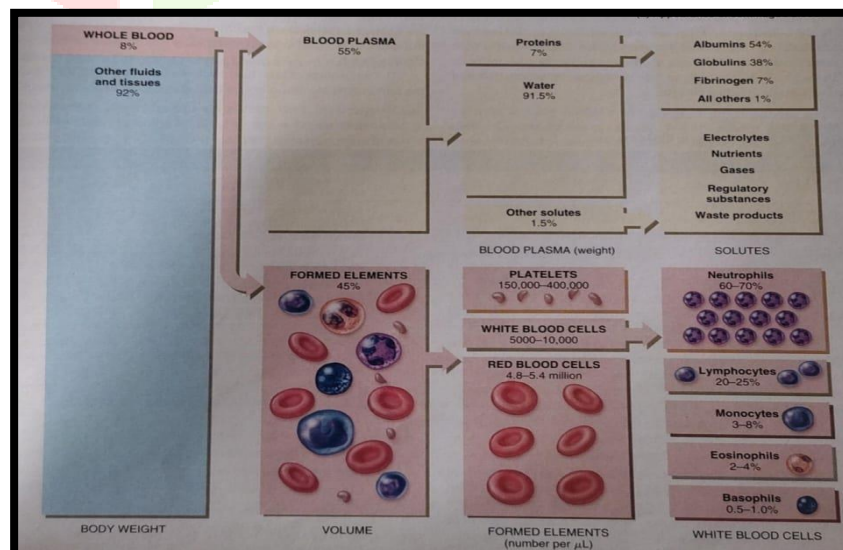


Fig 3. Components of Blood. (5)

1. Blood Plasma:

- The main constituent of plasma is water (90-92%).
- Blood plasma is pale yellow colored fluid and its total volume in adult approximately 2.5-3 liters.
- Plasma constituents approximately 55% of blood volume.
- It contains 8% to 9% of solids, organic and inorganic substances are the solids. (3,5)

The constituent of blood plasma: -

- a) Plasma proteins (7% of plasma).
- b) Hormones.
- c) Electrolyte.
- d) Nutrients, principally digested food.
- e) Waste products.
- f) Gases.

Plasma proteins: - Proteins of blood plasma found elsewhere in the body, those confined to blood known as plasma proteins. Most plasma synthesize in liver, with notable exception Immunoglobulins, which are produced by β - cells of immune system. (5)

Because they are too big to pass through the capillary wall into the tissue, Plasma protein retains blood stream and are the main factor to maintaining the osmotic pressure of blood, which control water distribution between plasma and tissue.

Hepatocytes produce most plasma proteins which include, the main groups of plasma proteins are albumin, globulins and clotting protein fibrinogen. Disc plasma proteins are also called antibodies or immunoglobulins, because they are produced during certain immune response. (3,5)

- **Albumin:** - Maintaining plasma osmotic pressure is the primary function of the most prevalent plasma protein, which makes up over 60% of the total. It also serves as a carrier molecule for steroid hormones, free fatty acids, and certain medications.
- **Globulins:** - The main function of globulins is as Antibodies (Immunoglobulins) and Transportation of some hormones and minerals salts.
- **Fibrinogen and other clotting factors:** - The main cation (positively charged ion) in blood is sodium (Na^+) and the main anion (negatively charged ion) is chloride (Cl^-). Electrolytes have a range of functions, including muscle contraction (e.g. Ca^{2+}), transmission of nerve impulses (e.g. Ca^{2+} , K^+ and Na^+), and maintenance of acid-based balance (e.g. phosphate, PO_4). Blood pH is maintained between 7.35 and 7.45 (slightly alkaline) by an ongoing buffering system. (3,5)

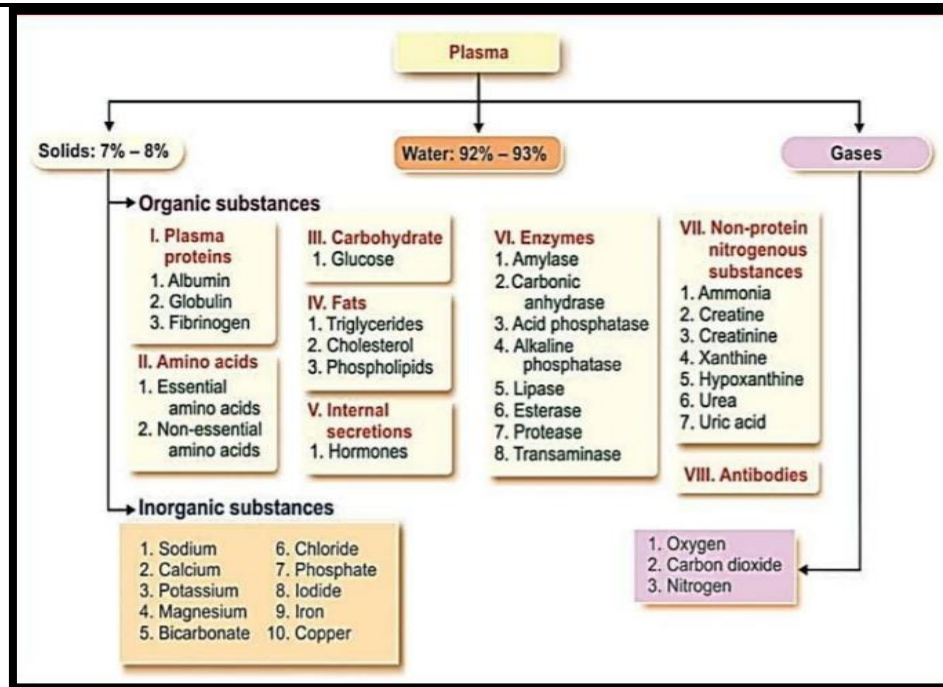


Fig 4. Composition of Plasma. (3)

2. Formed Element:

It is also known as cellular content of blood.

The formed element of blood includes--

- 1.Red blood cells.
- 2.White blood cells.
- 3.Platelet or Thrombocytes.

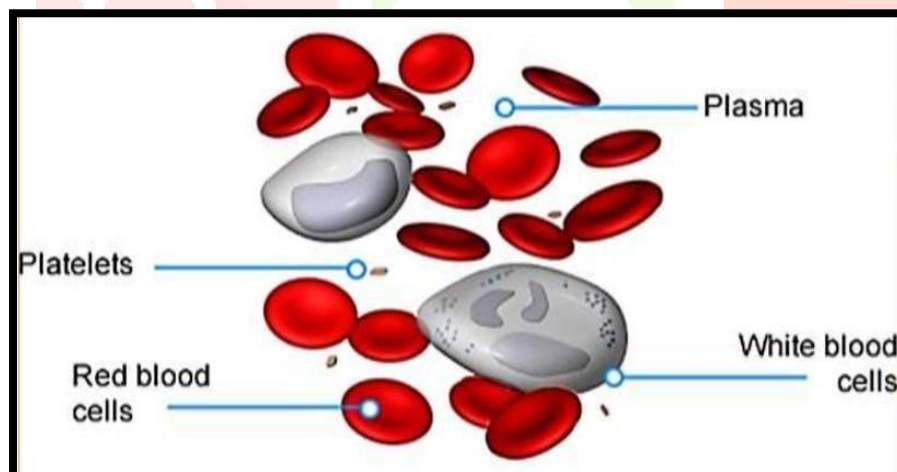


Fig 5. Blood Formed Element. (3)

Formation of blood cells:

Negative feedback regulates the total number of RBCs and platelets in circulation, and their numbers normally remain steady. However, the various WBC types of levels vary in response to attacks from external antigens and invading infections. The formation of the blood component elements is known as haemopoiesis. The yolk sac of an embryo undergoes haemopoiesis prior to birth, followed by the fetus's liver, spleen, thymus, and lymph nodes.

Red bone marrow has become the primary site of hemopoiesis in the last 3 months before birth and continues as the source of blood cells after birth.

Within bone marrow all blood cells originate from a single type of specialized cell called a stem cell. The myeloid stem cells are further subdivided in the bone marrow to produce red blood cells platelets, basophils, eosinophils, neutrophils and monocytes. (5)

Division of myeloid stem cell:

It first becomes an immature red blood cell, white blood cells and platelet producing cells. The immature cells then divide matures cells further and finally becomes the mature at blood says white blood cells or platelets. The lymphoid stem cell begins the development in the bone marrow as β and T -lymphocytes.

β - lymphocytes continue development in the bone marrow, before migrating to other lymph organs such as lymph nodes, spleen or tonsils. T-lymphocytes continue their development in the thymus and may then migrate to other living tissue. (5)

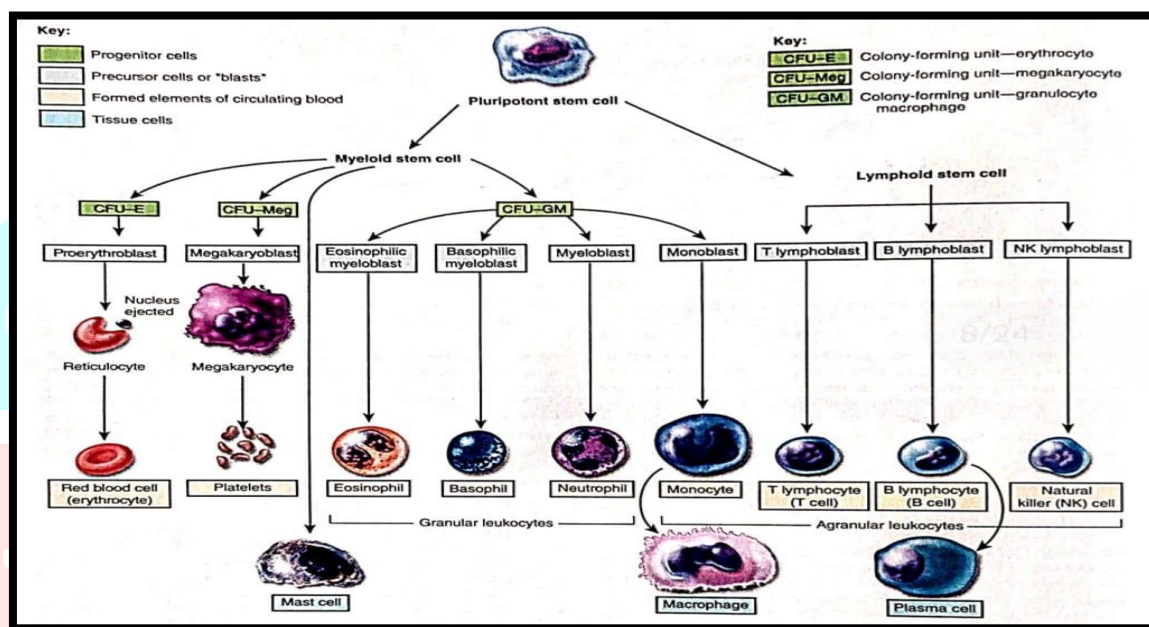


Fig 6. Origin, development and structure of blood cells. (5)

1. Red blood cells or Erythrocytes: -

The nature of human erythrocytes is circular, biconcave, non-nucleated disc shaped. The edges are rounded and thicker than the center.

The red blood cells or Erythrocytes contain oxygen-carrying protein hemoglobin, which is a pigment that gives whole blood to red color. (5, 6)

Normal red blood cells count:

A healthy adult male has about 5.4 million red blood cell per microliter of blood. And healthy adult female has about 4.8 million. In infants the number is 6-8 million, whereas in children 3-5 million per microliter of blood. To maintain the normal number of RBC, new mature cells must enter the circulation at the astonishing rate of at least 2 million per second. (6)

Anatomy of RBC:

RBCs are biconcave discs with a diameter of 7-8 μm . As mature red blood cells squeeze into small blood capillaries, their basic structure and strong, flexible plasma membrane enable them to break down without

rupturing. Several glycolipids found in the plasma membrane of red blood cells are antigens that explain the different blood types, including the ABO and Rh groups. Although they lack a nucleus and other organelles, red blood cells are unable to reproduce or perform complex metabolic processes. Hemoglobin molecules are found in the cytoplasm of red blood cells (RBCs). These crucial molecules are produced prior to the nucleus being lost during RBC synthesis and make up roughly 33% of the cell's weight. (6).

Physiology of RBC:

The oxygen transport carried out by red blood cells requires a high level of specialization. Mature red blood cells have no nucleus, so oxygen can move through their entire interior. The oxygen that RBCs carry is not used up since they do not have mitochondria and produce ATP anaerobically, or without oxygen. The function of an RBC is even facilitated by its form. The surface area of a biconcave disc is significantly larger than that of a sphere or cube, which would allow gas molecules to diffuse into and out of the RBC. About 280 million hemoglobin molecules are found in each red blood cell. The four polypeptide chains that make up a hemoglobin molecule are two alpha and two beta chains of the protein globin, to which a ring-shaped nonprotein pigment known as a hem is attached to four chains (6).

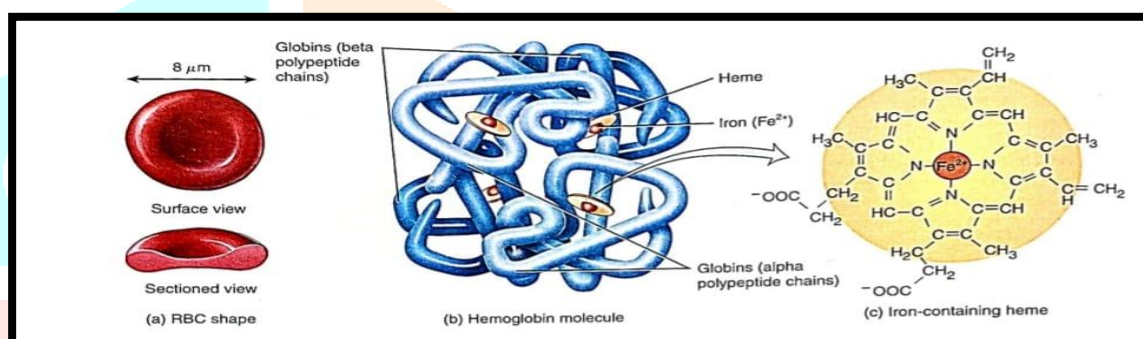


Fig 7. The shape of RBC and hemoglobin molecules. (5)

Stages of development of Erythrocytes:

The precursor cell known as a proerythroblast is where erythropoiesis, or the synthesis of red blood cells, begins in the red bone marrow. Multiple divisions of the proerythroblast result in cells that start to make haemoglobin. A cell approaching the end of the development process eventually becomes a reticulocyte by ejecting its nucleus. When the nucleus is lost, the centre of the cell indents, giving the red blood cell its characteristic biconcave form. Reticulocytes still have some endoplasmic reticulum, ribosomes, and mitochondria. They pass from red bone marrow into the bloodstream by squeezing between plasma membranes of adjacent endothelial cells of blood capillaries, reticulocytes develop into mature red blood cells within 1 to 2 days after their release from red bone marrow. (6)

2. White Blood Cells or Leucocytes: -

White blood cells or leukocytes have a nuclei and full complement of other organelles, but they do not contain haemoglobin. They have an important function in immunity and defence system. It detects foreign and abnormal materials and destroys them. Leucocytes are the largest blood cell with a count for only about 1% of the blood volume. Because they are much less numerous than erythrocytes. They contain nuclei and some granules in their cytoplasm. (3,5)

Table No.1. Normal leukocytes count in adult blood. (5)

	Number x 10 ⁹ /L	Percentage of total
Neutrophils	2.5-7.5	40-75
Eosinophils	0.04-0.44	1-6
Basophils	0.015-0.1	< 1
Monocytes	0.2-0.8	2-10
Lymphocytes	1.5-3.5	20-50
Total	5-9	100

Types of white blood cells or leucocytes:

There is main two types—

A. Granulocyte (Polymorphonuclear Leucocytes)

Neutrophils eosinophils and basophils.

B. Agranulocytes: - Monocytes and lymphocytes.

A. Granulocyte (polymorphonuclear leukocytes)-

During the formation it is known as granulopoiesis. They follow common line of development through myeloblast to myelocyte before differentiating into three. All Granulocytes have complex, multilobed nuclei in their cytoplasm. Their name reflects their dyes they take up when stained in laboratory.

Eosinophils take up red acid dye eosin.

Basophils absorb alkaline methylene blue.

Neutrophils are purple because they take both dyes. (3)

- Eosinophils: - The large, uniform sized granules within eosinophils are eosinophilic. They stain red, orange with acidic dye. They capable of phagocytosis, are less active in this process than neutrophils their role appears to be in elimination of parasite. The granules usually don't cover the nucleus., which most often has two lobes connected by either thin strand or thick strand of nuclear material. Local accumulation of eosinophils may occur in allergic inflammation such as asthmatic airways and skin allergy (3,5)
- Basophils: - A basophil's spherical, variable-sized granules are basophilic; basic dyes cause them to shade blue purple. The granules commonly obscure the nucleus, which has two lobes. (5)
- Neutrophils: - The granules of neutrophils are uniformly dispersed, pale lilac, and smaller than those of other granular leukocytes. Because the granules do not strongly attract either the acidic (red) or basic (blue) stain, these WBCs are neutrophilic (neuter loving). Two to five lobes make up the nucleus, which is joined by extremely thin nuclear material threads. The number of nuclear lobes in cells grows with age. Because older neutrophils thus have several differently shaped nuclear lobes, they are often called polymorphonuclear leukocytes (PMNs), polymorphs, or "polys."(5)

B. Agranulocytes-

Monocytes and lymphocytes together make up of 25 -50 % of total leukocytes count. They lack cytoplasmic granules and have a big nucleus.

Monocytes: - Among the white blood cells, these are the biggest. Shortly after release from the red bone marrow, they migrate into the tissues and develop into macrophages. Macrophages have crucial roles in immunity and

inflammation. Both monocytes and macrophages produce interleukin 1, which acts on the hypothalamus, causing the fever (pyrexia) associated with microbial infections. Interleukin 1 is therefore called pyrogen. It stimulates the production of some globulins by the liver, including fibrinogen, complement proteins, and inflammatory markers, and enhances the production of activated T-cells, which are important in immunity. (3)

- Lymphocytes: -The nucleus of a lymphocyte stains dark and is round or slightly indented. The cytoplasm envelopes the nucleus in a ring and stains sky blue. The amount of visible cytoplasm increases with cell size. Lymphocytes are classified by cell diameter as large lymphocytes (10-14 μm) or small lymphocytes (6-9 μm). Although the functional significance of the size difference between small and large lymphocytes is unclear, the distinction is still clinically useful because an increase in the number of large lymphocytes has diagnostic significance in acute viral infections and in some immunodeficiency diseases. (5)

3. Platelets: -

Besides the immature cell types that develop into erythrocytes and leukocytes, hemopoietic stem cells also differentiate into cells that produce platelets. The hormone thrombopoietin causes myeloid stem cells to differentiate into megakaryocyte colony-forming cells, which then differentiate into megakaryoblasts, which are progenitor cells. Megakaryoblasts develop into megakaryocytes, which are huge cells that break into two to three thousand pieces. Each fragment is a platelet and is surrounded by a section of plasma membrane. After separating from the red bone marrow's megakaryocytes, platelets enter the bloodstream.

Platelets are small (1-4 μm in diameter), discoid, non-nucleate structures containing red-purple granules. The normal platelet counts range from 150,000 to 400,000/ μl , and the lifespan of platelets is 7-10 days. About 70% of platelets are in circulation, while the remaining 30% are sequestered in the spleen. Newly formed platelets spend 24-36 hours in the spleen before being released into circulation, but splenic stasis does not cause any injury to the platelets normally. Factors such as stress, epinephrine and exercise stimulate platelet production. (7)

Haemostasis:

It is a sequence response to stop bleeding. When blood vessels are damaged or ruptured, blood losses stopped, and healing occurs in the series of the overlapping process in which platelets play vital role.

The haemostatic response must be quick and localised to the region of damage and carefully controlled to effective site. The successful Haemostasis prevents hemorrhage, the loss of large amount blood in the vessels. (3,5)

Three mechanisms to reduce blood loss:

1. Vascular spasm.
2. Platelet plug formation.
3. Blood clotting.

1. Vascular spasm: - Vascular spasm is a response to injury to arteries or arterioles, where the smooth muscle in the walls contracts instantly. For a few minutes to several hours, this lessens blood loss; during this period, the other haemostatic processes start working. Damage to the smooth muscle, chemicals released by activated platelets and reflexes triggered by pain receptors are most likely the causes of the spasm.

2. Platelet plug formation: - Considering their small size, platelets store an impressive formation of chemicals. Clotting factors, ADP, ATP, Ca^{2+} , and serotonin are found in several vesicles. There are additionally lysosomes, some mitochondria, membrane systems that absorb and store calcium, channels for the release of granule and glycogen contents, and enzymes that generate coagulant A_2 , a prostaglandin, and fibrin-stabilizing factor, which aids in forming a blood clot. Also within platelets is platelet derived growth factor (PDGF), a hormone that can cause proliferation of vascular endothelial cells, vascular smooth muscle fibres and fibroblasts to help repair damaged blood vessel walls. (5)

Platelet plug formation occurs as follows: -

- 1) In a ruptured blood vessel, platelets first encounter and bind to collagen fibers in the connective tissue beneath the injured endothelial cells. We refer to this phenomenon as platelet adhesion.
- 2) The platelets get activated because of adhesion, and their properties significantly alter. They start releasing the contents of their vehicles and extend many projections that allow them to communicate and exchange information. This refers to the process as the platelet release reaction. Because they activate neighboring platelets, released ADP and thromboxane A_2 are important. By generating and maintaining vascular smooth muscle contraction, serotonin and thromboxane A_2 function as vasoconstrictors, reducing blood flow through the damaged vessel.
- 3) The newly recruited and activated platelets attach to the first activated platelets because the release of ADP makes additional platelets in the surrounding area sticky. Platelet aggregation refers to this collection of platelets. Eventually, the accumulation and attachment of large numbers of platelets form a mass called a platelet plug. (5,6)

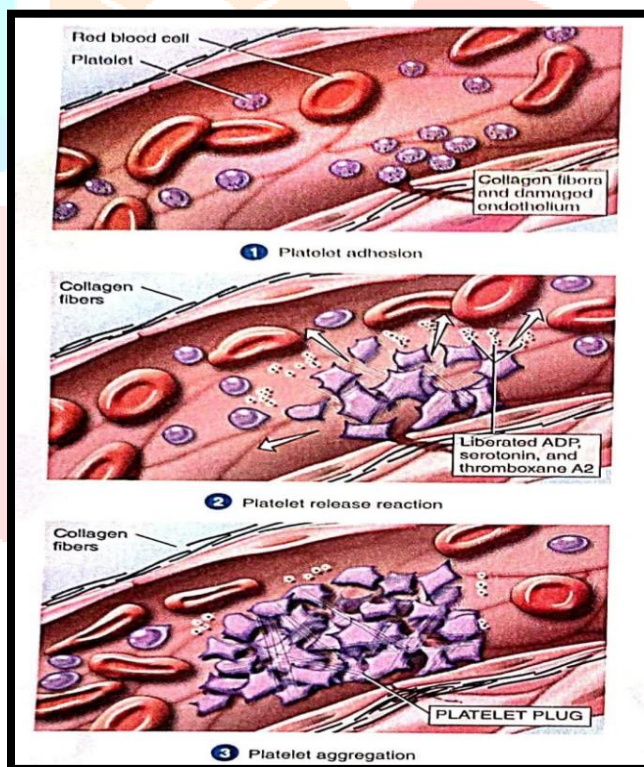


Fig 9. Platelet Plug Formation. (5)

4. Blood Clotting: - When blood shed it loses its fluidity in a few minutes and sets into semisolid jelly this is known as blood coagulation or clotting. Normally, blood remains in its liquid form if it stays within its vessels. However, it thickens and turns into a gel if it is extracted from the body. Eventually, the gel separates from the liquid. The straw-coloured liquid called as serum, is simply blood plasma minus the clotting proteins. The gel is called a blood clot. It consists of insoluble network of insoluble protein fibres known as fibrin, in which formed elements are trapped.

Clotting involves several substances known as clotting factors. These factors which include calcium ions (Ca), several inactive enzymes that are synthesized by hepatocytes (liver cells) and released into the bloodstream and various molecules associated with platelets or released by damaged tissues. Most clotting factors are identified by Roman numerals that indicate the order of their discovery. (5)

Clotting is a complex cascade of enzymatic reactions in which clotting factor activates many molecules of the next one in a fixed sequence. Finally, a large quantity of product is formed.

Clotting can be divided into stages:

- In pathway it firstly, lead to the formation of prothrombinase. The subsequent two stages of clotting, which are known as the common pathway, include the identical actions for both the intrinsic and extrinsic pathways once prothrombinase is produced.
- Prothrombinase transforms the liver-produced plasma protein prothrombin into the enzyme thrombin, while thrombin transforms the liver-produced plasma protein soluble fibrinogen into insoluble fibrin. The threads of the cloth are made of fibrin. (5.6)

There are mainly two pathways which are included in the blood coagulation process.

- Extrinsic Pathway.
- Intrinsic Pathway.

Table No. 2. Blood coagulation factors.
(5)

Number	Name(s)	Source	Pathway(s) of Activations.
I	Fibrinogen.	Liver	Common
II	Prothrombin.	Liver	Common
III	Tissue factor (thromboplastin).	Damage tissue and activated platelets.	Extrinsic
IV	Calcium ions (Ca ²⁺).	Diet, Bones and Platelets.	All
V	Proaccelerin, labile factor, or accelerator globulin (ACG).	Liver and Platelets.	Extrinsic and Intrinsic
VII	Serum prothrombin conversion accelerator (SPCA), stable factor, or proconvertin.	Liver	Extrinsic
VIII	Antihemophilic factor (AHF), antihemophilic factor A, or antihemophilic globulin (AHG).	Liver	Intrinsic
IX	Christmas factor, plasma thromboplastin component (PTC), or antihemophilic factor B.	Liver	Intrinsic
X	Stuart factor, Power factor, or thrombokinase.	Liver	Extrinsic and Intrinsic

XI	Plasma thromboplastin antecedent (PTA) or antihemophilic factor C.	Liver	Intrinsic
XII	Hageman factor, glass factor, contact factor, or antihemophilic factor D.	Liver	Intrinsic
XIII	Fibrin-stabilizing factor (FSF).	Liver and platelets	Common

i. Extrinsic Pathway: -

The extrinsic pathway of blood clotting has fewer steps than the intrinsic pathway and occurs within a matter of seconds if trauma is severe. It is so named because a tissue protein called tissue factor (TF) is also known as thromboplastin.

Step 1- The tissue factor or thromboplastin is released from the tissue injury.

Step 2- Factor VII activation.

Tissue thromboplastin converts factor VII to factor VIIa which directly activates factor and factor IX and factor X.

Step 3- Factor X activation.

The factor VIIa converts factor X to factor Xa in presence of calcium, tissue thromboplastin and platelet phospholipids. (5,6)

ii. Intrinsic Pathway: -

In the intrinsic pathway, blood clotting is more complex than the extrinsic pathway and it occurs more slowly, usually requiring several minutes.

The intrinsic pathway is named because its activators are either in direct contact with blood or contained in the blood.

Step 1- Factor XII activation.

The contact of factor XII with exposed collagen of blood vessels or with negative charge surface activates which leads to the intrinsic pathway. The factor XII which facilitates or activates the factor XIIa are cofactor high molecular weight kininogen and kallikrein.

Step 2- Factor XI activation.

The factor XIIa converts factor XI to activated form as XIa in presences of high molecular weight kininogen.

Step 3- Factor IX activation.

Factor XIa converts factor IX to activated form.

Step 4- Factor X activation.

Factor IXa activates factor X to Xa in presence of cofactor activated factor VIII, calcium and membrane phospholipids. (5,6)

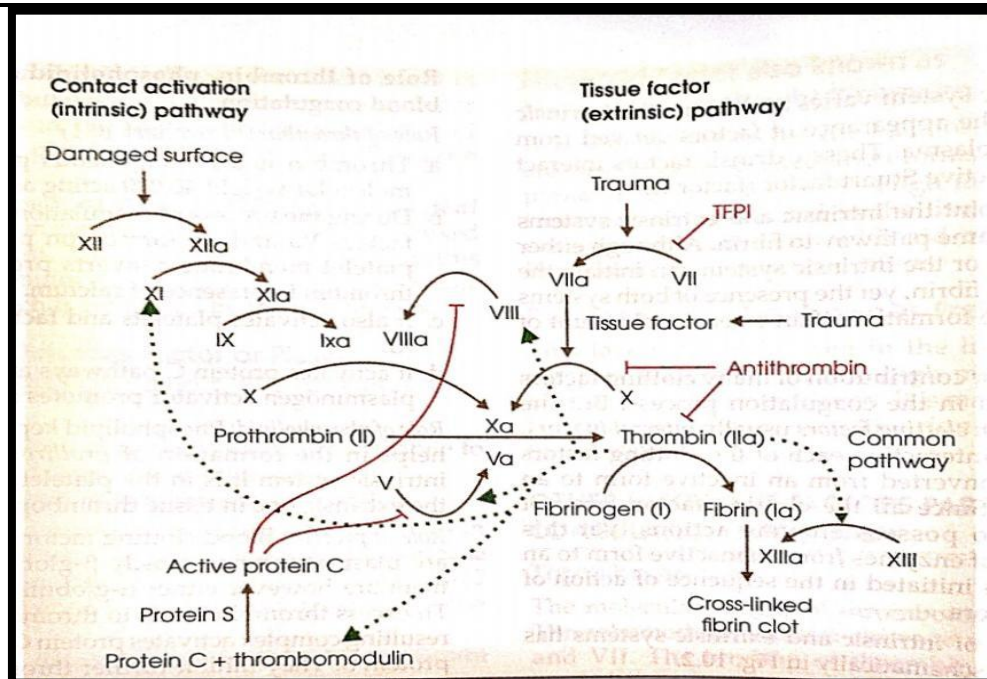


Fig 11. Mechanism of intrinsic and extrinsic blood coagulation. (5)

The Common Pathway:

The common pathway begins with the production of prothrombinase. In the second stage of blood clotting, prothrombinase and Ca catalyse the conversion of prothrombin to thrombin. In the third stage, thrombin, the presence of Ca, converts fibrinogen, which is soluble, to lose fibrin threads, which are insoluble. Thrombin also activates factor XII (fibrin stabilizing factor), which strengthens and stabilizes the fibrin threads into a sturdy clot. Factor XIII is present in plasma and is also released by platelets that become trapped in the clot. There are two beneficial effects of thrombin. It speeds up prothrombinase synthesis in the first beneficial feedback loop, which involves factor V. More thrombin is produced more quickly by prothrombinase, and so forth. In the second positive feedback loop, thrombin activates platelets, which reinforces their aggregation and the release of platelet phospholipids. (5,6)

Clot Retraction:

Once a clot is formed, it plugs the ruptured area of the blood vessel and thus stops blood loss it is called as Clot retraction. The fibrin clot's tightening or consolidation. As platelets strain on the injured blood vessel surfaces, the fibrin threads that attach to them gradually shrink. The risk of more injury is reduced as the clot retracts, pressing the injured vessel's margins closer together. Some serum may be able to pass through the fibrin threads during retraction, but the blood's produced components are unable. Enough platelets in the clot is necessary for normal retraction since these platelets produce factor XIII and other substances that help stabilize and strengthen the clot. After that, the blood vessel can be properly repaired.

In time, fibroblasts form connective tissue in the ruptured area, and new endothelial cells repair the vessel lining. (5)

Haemostatic control mechanism:

Fibrinolysis -

If clotted blood remains sterile, it will stay unchanged for a few weeks. However, if it is not maintained sterile, the clot breaks down. In human body the blood coagulation initiates the blood anti-clotting mechanism by activation of protein C and plasmin. Thrombin and so also thrombomodulin activate protein C into its active

form. The protein C inactivates the inhibitors of plasmin activators. This activates plasminogen activator which converts plasminogen into plasmin. So, with the help of cofactor protein S inactivates factors Va and VIIa and prevents coagulation. Thus, fibrin breakdown in the clot which is known as fibrinolysis is brought about by a proteolytic enzyme in the plasma known as plasmin or fibrinolysin. The fibrin is degraded by plasmin into fibrin degradation products. Normally fibrinolysis is prevented by the presence of another substance in the blood known as anti-plasmin which remains attached to the plasma albumin clotting, clot formation normally remains localized at the site of damage. Because fibrin absorbs thrombin into the clot, a clot does not spread beyond the wound site into the bloodstream. Another reason for localized clot formation is that because of the dispersal of some of the clotting factors by the blood, their concentrations are not high enough to bring about widespread clotting. Several other mechanisms also control blood clotting. For example, endothelial cells and white blood cells produce a prostaglandin called prostacyclin that opposes the actions of thromboxane A₂. Prostacyclin is a powerful inhibitor of platelet adhesion and release it.

In addition, substances that delay, suppress, or prevent blood clotting, called Anticoagulants. (6)

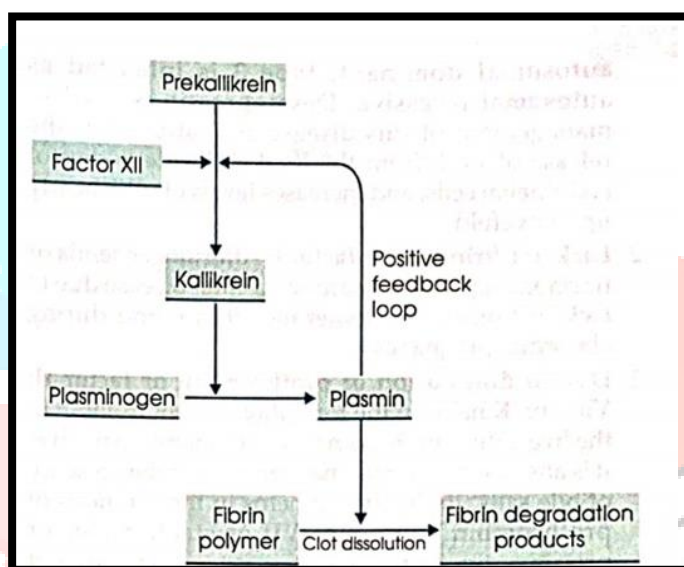


Fig. Fibrinolysis (6)

• Coronary Arteries Diseases (CAD)-

When the myocardium does not receive enough blood and oxygen, it is known as coronary artery disease. It arises from a mismatch between the supply and demand of oxygen due to coronary artery blockage. It typically involves the formation of plaques in the lumen of coronary arteries that impede blood flow. (7)

Pathophysiology of CAD:

The hallmark of the pathophysiology of CAD is the development of atherosclerotic plaque. Plaque is a buildup of adipose material that narrows the vessel lumen and impedes the blood inflow. The first step in the process is the conformation of adipose band. Adipose band is formed by subendothelial deposit of lipid laden macrophages, also called foamy cells. When a vascular injury occurs, the intima sublayer breaks, and monocytes resettle into the subendothelial space where they become macrophages. These macrophages take up oxidized low density (viscosity) lipoprotein (LDL) particles, and foamy cells are formed. T cells get activated, which releases cytokines only to propel the pathologic process. Growth factors released stimulate smooth muscles, which also take up oxidized LDL particles and collagen and deposit along with activated macrophages and increase the population of foamy cells. This process leads to the conformation of subendothelial plaque. Over

time, this shrine could grow or come stable if no farther personality occurs to the endothelium. However, a stringy cap will form, and the lesion will come calcified over time, if it becomes stable. As time passes, the lesion can come hemodynamically significant enough that not enough blood would reach the myocardial towel at the time of increased demands, and angina symptoms would do still, symptoms would abate at rest as the oxygen demand comes down. For a lesion to beget angina at rest, it must be at least 90 stenosed. Some pillars can rupture and lead to exposure of towel factor, which culminates in thrombosis. This thrombosis could beget subtotal or total occlusion of the lumen and could affect in the development of acute coronary pattern (ACS) in the form of unstable angina, NSTEMI, or STEMI, depending on the position of personality. (7,8)

• Stroke-

A stroke is an abrupt loss of brain function brought on by an obstruction in the central nervous system's (CNS) blood supply. A cerebral blood flow (CBF) of 50–60 ml/100 g/min is considered normal. A decrease in CBF of less than 10 ml/100 g/min results in irreparable neuronal damage, while a decrease of less than 20 ml/100 g/min produces electrical silence. When blood flow to the brain is disrupted, neurons are deprived of oxygen and glucose. Because they send impulses, neurons need a steady flow of energy. An ischemic stroke can account for up to 85% of all strokes; the majority are caused by blood clots blocking one or more cerebral arteries, which lowers brain perfusion. The remaining stroke instances are hemorrhagic, meaning they involve either subarachnoid or intracerebral hemorrhage. Ischemic stroke may manifest in the form of thrombotic stroke (9,10)

Pathophysiology of Stroke:

Energy failure, loss of cell ion homeostasis, acidosis, elevated intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, production of arachidonic acid products, cytokine-mediated cytotoxicity, complement activation, disruption of the blood-brain barrier (BBB), activation of glial cells, and leukocyte infiltration are just a few of the numerous processes that contribute to the complex pathophysiology of stroke. These are interrelated and co-ordinated events, which can lead to ischemic necrosis, which occurs in the oppressively affected ischemic- core regions. Within many minutes of a cerebral ischemia, the core of brain tissue exposed to the most dramatic blood flow reduction, is mortally injured, and latterly undergoes necrotic cell death. This necrotic core is girdled by a zone of lower severely affected tissue which is rendered functionally silent by reduced blood flow but remains metabolically. Necrosis is morphologically characterized by original cellular and organelle lump, posterior disruption of nuclear, organelle, and plasma membranes, decomposition of nuclear structure and cytoplasmic organelles with extrusion of cell contents into the extracellular space. The region bordering the infarct core, known as the ischemic penumbra, comprises as important as half of the total lesion volume during the original stages of ischemia, and represents the region in which there's opportunity for salvage via post-stroke therapy. Less severe ischemia, as occurs in the penumbra region of a focal ischemic infarct, evolves more slowly, and depends on the activation of specific genes and may ultimately affect in apoptosis (9,10). Recent exploration has revealed that numerous neurons in the ischemic penumbra, or peri-infarct zone, may undergo apoptosis only after several hours or days, and therefore they're potentially recoverable for some time after the onset of stroke. In contrast to necrosis, apoptosis appears to be an orderly process of energy-dependent programmed cell death to dispose of spare cells. Cells undergoing apoptosis are dismantled from within in a systematized way that minimizes damage and disruption to bordering cells. There are two general pathways for activation of apoptosis the natural and foreign pathways. (11,12)

• Atherosclerosis-

Atherosclerosis (also known as Arteriosclerotic Vascular Disease or ASVD) it is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. The accumulation of macrophage white blood cells and low density (especially small particle) lipoproteins (plasma proteins that carry cholesterol and triglycerides) without sufficient removal of fats and cholesterol from the macrophages by functional high-density lipoproteins (HDL) are the main causes of this syndrome, which affects arterial blood vessels and causes a chronic inflammatory response in the artery walls. This condition is commonly referred to

as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries. (13,14)

Pathophysiology of ASVD

There are 2 Steps: -

1. Plaque formation.

Atherosclerosis begins when the injured artery coronary wall creates chemical signals that cause certain types of white blood cells (monocytes and T cells) to attach to the wall of the artery. These cells are incorporated into the arterial wall. Their transformation into foam cells causes the arterial wall's smooth muscle cells to proliferate while also accumulating cholesterol and other fatty substances. In time, these fat-laden foam cells accumulate. They form patchy deposits (atheroma's, also called plaques) covered with a fibrous cap in the Atherosclerotic Plaque lining of the artery wall. With time, calcium accumulates in the plaques. Plaques may be scattered throughout medium-sized and large arteries, but they usually start where the arteries branch. (15,16)

2. Plaque rupture.

The artery may gradually narrow because of plaques growing into its lumen. An artery's ability to supply tissues with blood and oxygen may be compromised when atherosclerosis causes the artery to narrow. Plaques can also develop into the arterial wall, where they do not obstruct blood flow. Both types of plaques have the potential to rupture, or break open, allowing the bloodstream to see the contents. This substance causes blood clots to develop. The primary cause of a heart attack or stroke is the sudden blockage of all blood flow through the artery caused by these blood clots. These blood clots can occasionally separate, move through the system, and obstruct an artery in another part of the body.

Similarly, pieces of the plaque can break off and travel through the bloodstream and block an artery elsewhere. (15,16)

ANTICOAGULATION

Natural anticoagulant Mechanism

Thrombin generation and fibrin formation occur rapidly at sites of vascular injury. To control and localise these processes, several inhibitory mechanisms are in place. Regulation of coagulation is exerted at multiple levels, either by enzyme inhibition or by modulation of the activity of the cofactors. The three most significant coagulation regulators are antithrombin, protein C, and protein S. Together with TFPI and the fibrinolytic system, they constitute the main natural anticoagulant and antithrombotic mechanisms in the organism. Thus, patients with a familial deficiency in one or the other of these components tend to develop thromboembolic complications (thrombophilia). Knowledge of natural coagulation inhibitors is guiding the development of several new anticoagulants.

Most of the enzymes generated during activation of coagulation are inhibited by the serine-protease inhibitor antithrombin (AT), previously called AT III. AT preferentially inhibits free enzymes, whereas enzymes that are part of the intrinsic tense or prothrombinase complexes are less accessible for inhibition. AT probably physiologically limits the coagulation process to sites of vascular injury and protects the circulation from liberated enzymes. AT is an inefficient inhibitor, but heparin and the heparin-like molecules that are present on the surface of endothelial cells stimulate its activity. Thrombomodulin (TM), a transmembrane molecule expressed on endothelial cells, binds thrombin, and the thrombin/TM complex activates protein C, a vitamin K-dependent proenzyme, to an active serine protease. (17)

The activated protein C (APC) anticoagulant system regulates coagulation by modulating the activity of the two cofactors, FVIIIa and FVa. The activation rate of thrombin-mediated protein C activation is slow but increased at least 100-fold when thrombin binds to TM. The rate increases another 20-fold when protein C binds to endothelial protein C receptor (EPCR), which presents protein C to the thrombin/TM complex for efficient activation, highlighting a mechanism for endothelial cell localisation of anticoagulation. Thus, thrombin has the

capacity to express both procoagulant and anticoagulant functions depending on the context under which it is generated. At sites of vascular disruption, the procoagulant effects of thrombin are fully expressed. In contrast, with an intact vascular system, thrombin has an anticoagulant function since it binds to TM and activates protein C. Another vitamin K-dependent cofactor protein, protein S, supports the anticoagulant activity of APC.

In human plasma, about 30% of protein S is free, the remainder being bound to the complement regulatory protein C4b-binding protein. APC and free protein S form a membrane-bound complex, which can cleave FVIIIa and FVa, even when these are part of the fully assembled intrinsic tenase and prothrombinase complexes. In vivo, APC does not cleave intact FVIII because the binding of FVIII to von Willebrand factor prevents it from interacting with the phospholipid membranes. In contrast, APC can cleave FV, which binds phospholipids to a similar extent as FVa. The consequence of APC-mediated cleavage of FV is the generation of anticoagulant FV that functions in synergy with protein S as an APC cofactor in the degradation of FVIIIa. Thus, FV can function as a procoagulant and an anticoagulant cofactor. Procoagulant FVa is formed after limited proteolysis by thrombin or FXa, whereas anticoagulant FV activity is expressed by FV that has been cleaved by APC. The anticoagulant potential of FV may be particularly important in the regulation of the intrinsic tenase complex by APC and protein S. The physiological importance of the protein C system is shown by the severe thromboembolic disease that is associated with homozygous deficiency of protein C or S in both humans and mice. (17)

In all situations, the deadly thrombotic illness appears soon after birth. Mice lacking a functional TM or EPCR gene have even more severe disease and die during embryogenesis, even before development of a functional cardiovascular system. Recombinant forms of soluble TM (recomodulin and solulin) and of APC (drotrecogin) have been developed as anticoagulants. In addition to activation of protein C, the thrombin/TM-complex also activates the thrombin activatable fibrinolysis inhibitor (TAFI), a latent carboxypeptidase. Once activated, TAFI slows the rate of fibrin degradation by removing the C-terminal lysine residues from fibrin. Because these lysine residues serve as binding sites for tissue-plasminogen activator (t-PA) and plasminogen, their removal renders fibrin more resistant to lysis. Decreased overall fibrinolytic potential, occurring in patients with congenital plasminogen, alpha2-antiplasmin or t-PA deficiency, or with high plasma levels of TAFI have been associated with the risk of venous thrombosis, whereas little evidence exists for their role in arterial thrombosis. Increased levels of plasminogen activator inhibitor (PAI)-1 have been conversely associated with arterial thrombosis. Several fibrinolytic proteins have activities that extend beyond fibrinolysis, such as inflammation, vascular remodelling, and atherosclerosis. (18)

Direct oral anticoagulant

DOACs are gradually replacing other anticoagulants to treat venous thromboembolism (VTE) patients. Now, the clinic prescribes four DOACs: rivaroxaban, apixaban, edoxaban, and dabigatran, which target thrombin and [FXa]. Since each medication blocks the active site of the target enzyme that is revealed upon activation, their modes of action are identical. Small synthetic compounds known as DOACs are taken orally. In comparison to VKAs, they are quickly absorbed into the bloodstream and significantly improve daily clinical practice due to their direct inhibition of coagulation proteins. Furthermore, DOACs are more predictable and require less stringent monitoring because they have a far lower number of contraindications with meals and other medications.

The neutralizing agent for dabigatran is a humanized Fab fragment of an antibody that directly binds dabigatran and neutralizes its activity. A recombinant protein called andexanet alpha may replicate the FXa active site without being able to participate in the formation of the prothrombinase complex, making it a decoy for FXa DOACs (however the effectiveness of edoxaban remains to be studied). Prothrombin complex concentrates (PCCs) can be given as a neutralizing agent to patients on rivaroxaban, apixaban, or edoxaban because andexanet alpha is a costly medication. PCCs avoid FXa DOACs because they work in the coagulation cascade downstream of FXa. The treatment of VTE has been greatly aided by DOACs for both patients and doctors, and

in the ensuing decades, DOACs will probably be prescribed more frequently in place of other anticoagulants. (17).

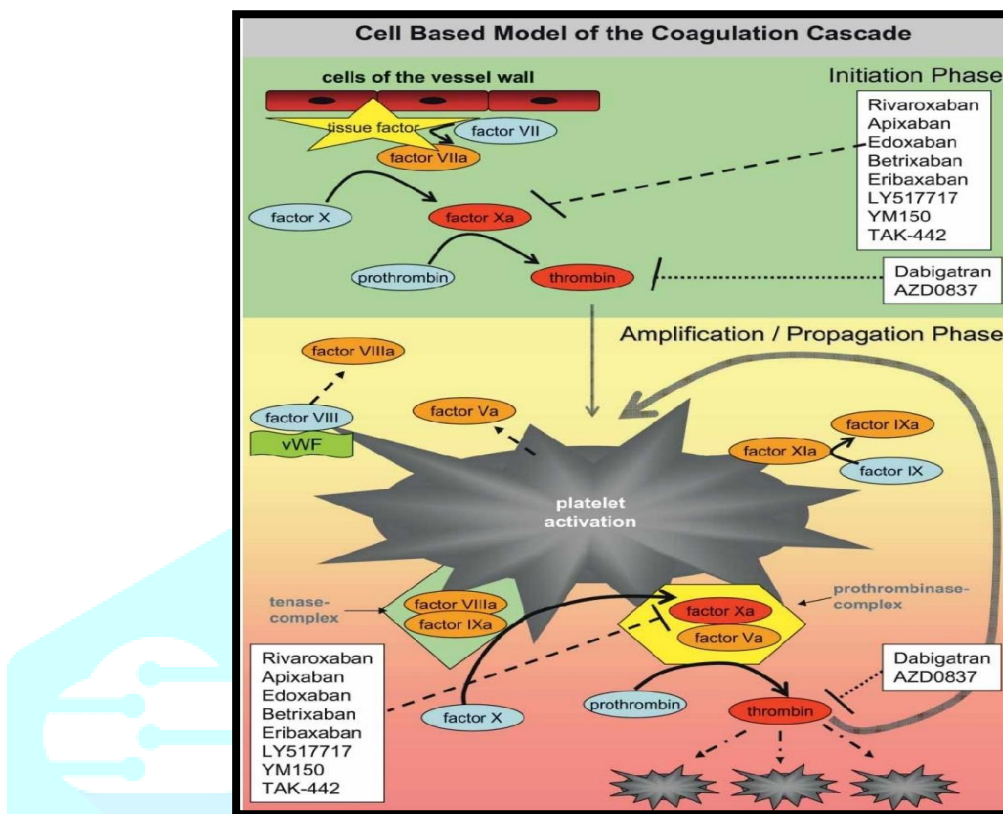


Fig. Cell Based Mode of Coagulation Cascade. (18)

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