THE CLOT THICKENS

By

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Abstract

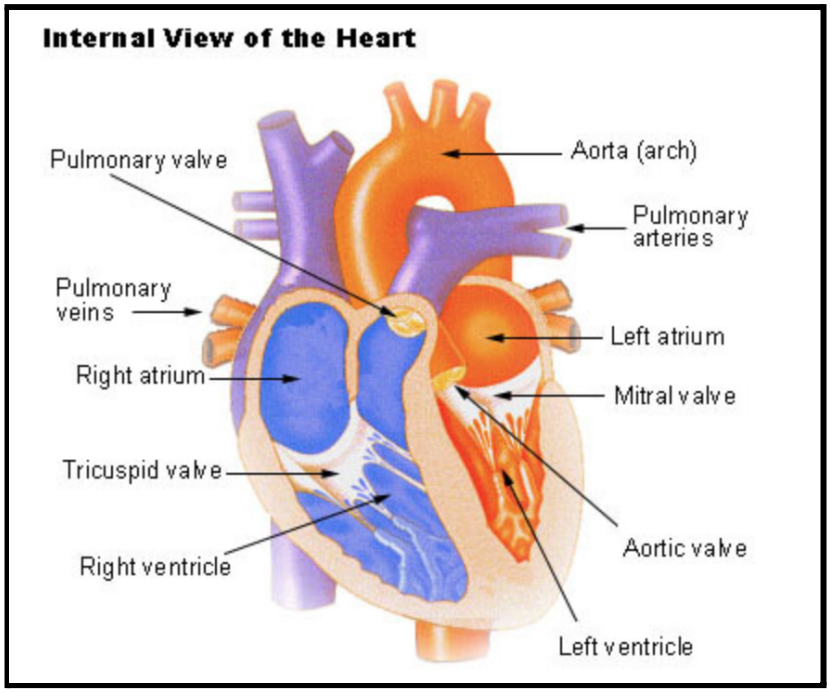
The cardiovascular system is made up of three components: the heart, the blood vessels, and blood. Each of these components has its own set of functions, but the heart and blood vessels main purpose is to pump and transport blood to the rest of the body. Blood carries oxygen, nutrients, medications, and hormones to all of the body's tissues, making it crucial that it reaches every organ in an organized fashion. Blood is also necessary in the wound-healing process, as it carries platelets, which are used for coagulation, and white blood cells, which are used in the immune response. When blood clots form that are not necessary for healing or to prevent blood loss, this could cause major issues for the body. If the clot dislodges and travels to the heart or brain, it could cause a heart attack or a stroke. It is important to understand how the coagulation process works in order to identify those who are at risk for developing these life-threatening conditions as well as seek treatment for those who are showing signs of a blood clot.

Intro to the Cardiovascular System

The Cardiovascular (CV) System consists of three main components: the heart, the blood vessels, and the blood itself. The CV System serves many functions: oxygen and nutrient delivery, maintenance of body temperature, and allowing the body to meet metabolic demands of exercise.[16]

The Heart

The heart is the main organ of the CV system and it serves as the body's pump. It pushes blood through the vessels in order to deliver oxygen and nutrients to the tissues of the body. It is a hollow organ made of cardiac muscle that sits directly in the center of the chest between the sternum and the vertebral column. It is separated into four chambers with two atria and two ventricles that help organize blood flow to obtain oxygen from the lungs and deliver it to the rest of the body. The heart is also responsible for generating blood pressure, which is essential for keeping blood circulating throughout the body.[27]



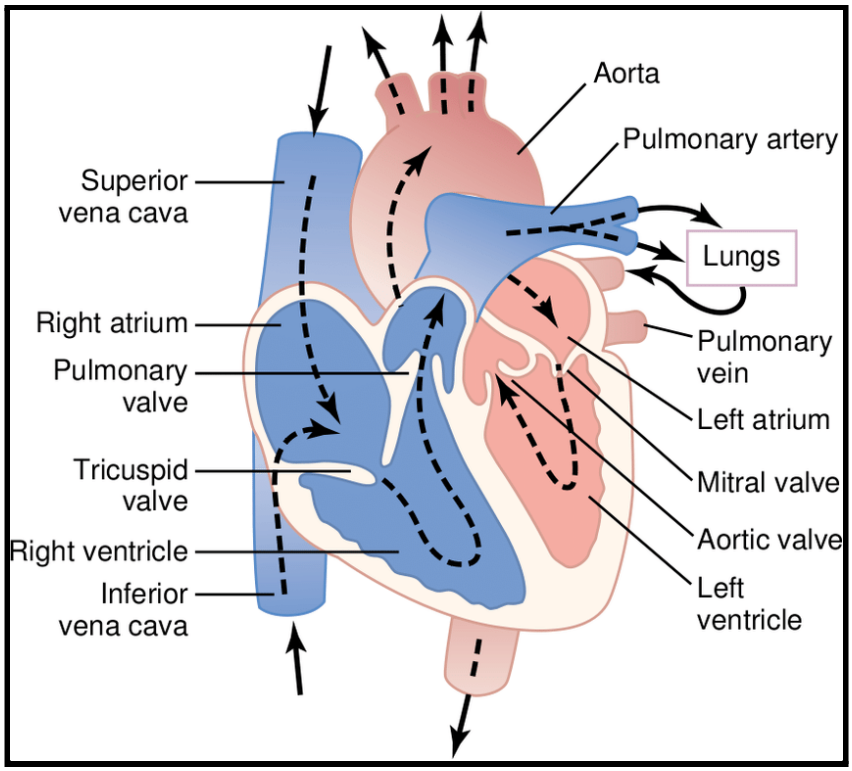
National Cancer Institute SEER Training Modules. *Internal View of the Heart*.; 2022. https://training.seer.cancer.gov/anatomy/cardiovascular/heart/structure.html

The Chambers of the Heart

The heart is a dual-pump with four chambers separated by the muscular septum into two sides, the right side of the heart, consisting of the right atrium and right ventricle and the left side of the heart, consisting of the left atrium and left ventricle. The right side of the heart is responsible for transporting blood to the lungs through the pulmonary circulation. Since the lungs are located right next to the heart, less muscle is required and consequently, the heart walls are much thinner and less muscular. The left side of the heart is responsible for pumping blood to the entire body through the systemic, or peripheral, circulation. Since the blood has much farther to go and sometimes has to fight gravity, the left ventricle has the thickest walls of any of the four chambers of the heart.[27]

Blood Flow Through the Heart

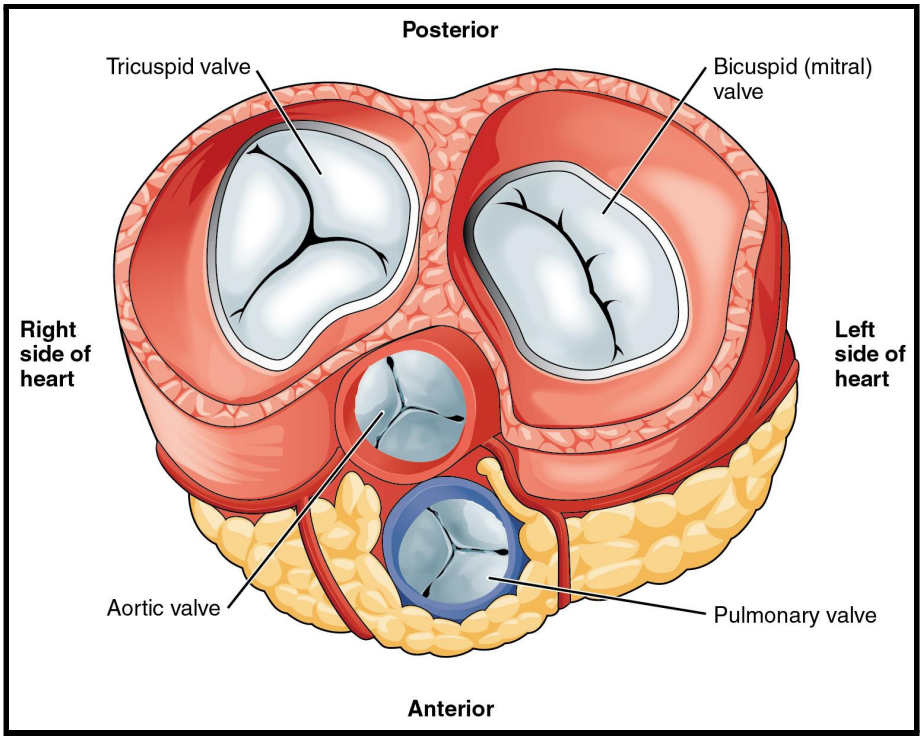
Blood flow through the heart begins with deoxygenated blood coming back from the body through the superior and inferior vena cavae which empties into the right atrium. It then travels through the tricuspid valve into the right ventricle. From there, blood exits the heart through the pulmonary valve and travels through the pulmonary arteries into the lungs, where it is oxygenated. It then re-enters the heart through the pulmonary veins which empty into the left atrium. Blood then travels through the bicuspid, or mitral, valve into the left ventricle. It is then pumped out through the aortic valve into systemic circulation via the aorta.[16]



Guyton & Hall Textbook of Medical Physiology. *Structure of the Heart. Blood Flow through the Chambers and Heart Valves.*; 2000. https://www.researchgate.net/figure/Structure-of-the-heart-Blood-flow-through-the-chambers-and-heart-valves-Figure_fig1_327558169

Heart Valves

The valves of the heart are separated into two categories: the Atrioventricular (AV) valves and the Semilunar (SL) valves. The AV valves are the tricuspid and bicuspid/mitral valves that separate the atria and the ventricles. The AV valves contain thin, fibrous chords or tendinous tissues, aptly called chordae tendineae. These chords are fastened to the wall of the heart by small papillary muscles that protrude from the inner surface of ventricular walls. The SL valves are the pulmonary and aortic valves that separate the ventricles from various vessels that take blood into either pulmonary or systemic circulation. The SL valves do not have chordae tendineae to help them snap shut, so instead they are composed of three cusps that create pockets that fill with blood when the valves close, which creates an extremely tight seal.[16]

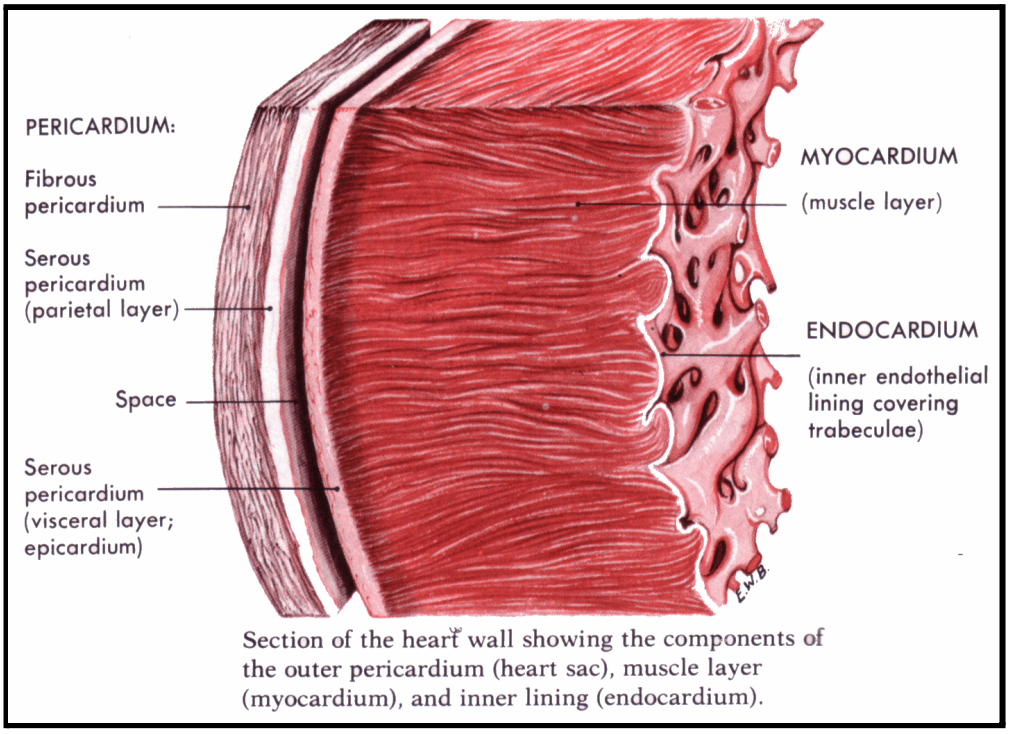


20. Wikimedia Commons. *Heart Valves*.; 2011. https://upload.wikimedia.org/wikipedia/commons/b/b9/2011_Heart_Valves.jpg

The Heart Wall

The wall of the heart is separated into three layers: the outermost pericardium, the myocardium, and the innermost endocardium. The pericardium is a double-walled sac that encloses the heart. It is composed of the visceral pericardium, also called the epicardium, and the parietal pericardium which are separated by a cavity full of pericardial fluid. The pericardium itself prevents the heart from moving in the thoracic cavity and protects it from acceleration and deceleration. It also provides an immune barrier that protects the heart from pathogens and contains pain and pressure sensors that will let the body know if something is wrong. The myocardium is the thickest layer of the heart wall and is composed of cardiac muscle and is anchored to the heart's fibrous skeleton. The endocardium is the inner layer of endothelial tissue and is the thinnest out of all of the heart

wall layers.[27] Endothelial tissue lines the entire CV System and interacts with blood and prevents it from getting too sticky while traveling through circulation.[16]



Socratic. *Section of the Heart Wall*.; 2016. https://socratic.org/questions/which-is-the-cardiac-muscle-layer-of-the-heart

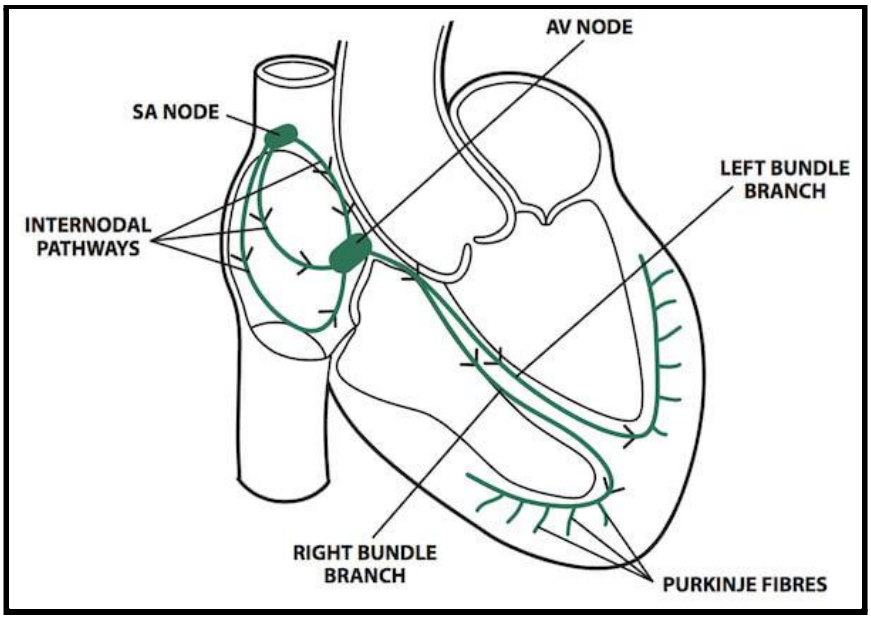
Cardiac Muscle

The heart is made of a special kind of muscle called cardiac muscle, which is only found in the heart. Cardiac muscle can be distinguished from other muscle types due to the presence of intercalated discs, which are structures that join cardiac muscle cells, or myocytes, together into branching fibers. Two types of structures are present within the intercalated discs that allow the cells to work as one when contracting: desmosomes and gap junctions. Desmosomes allow for tight connections between cells by connecting their cytoskeletons. Gap junctions connect opposing cell membranes and allow for the sharing of materials and cytoplasm between adjacent cells. It is necessary for the cardiac myocytes to work together when the heart is contracting so that both the left and right atria contract at

the same time and the left and right ventricles contract at the same time.[29] This creates what is called a functional syncytia, which means the muscle cells are acting as one.

Electrical Activity of the Heart

The heart is composed of three different types of cells: endothelial cells, which line the entire CV system, cardiac muscle cells, and cardiac conduction cells. Cardiac conduction cells, or pacemaker cells, are responsible for maintaining normal sinus rhythm of the heart and allows the heart to develop rhythm on its own, without neural input. The pacemaker cells set the pace of the heart and make up a variety of structures that allow the electrical signal to travel throughout the whole heart during contraction. The signal starts at the sinoatrial (SA) node which is located in the upper right corner of the right atrium. The SA node is the "pacemaker of the heart", and a heart beat is only considered "normal sinus rhythm" if the signal begins at the SA node. It then travels to the atrioventricular (AV) node, located in the bottom left corner of the right atrium. From there, the signal travels through the Bundle of His, (also called the AV bundle) down the septum, where it splits into two. It finally travels through fibers that are on the outsides of the ventricles, called the Purkinje Fibers. All of these structures are necessary for the heart to function as a dual pump and move blood in an organized fashion.[27]



Medical Exam Prep. *Cardiac Conduction System*.; 2016. https://www.medicalexamprep.co.uk/the-basics-of-ecg-interpretation-part-1-anatomy-and-physiology/cardiac-conduction-system/

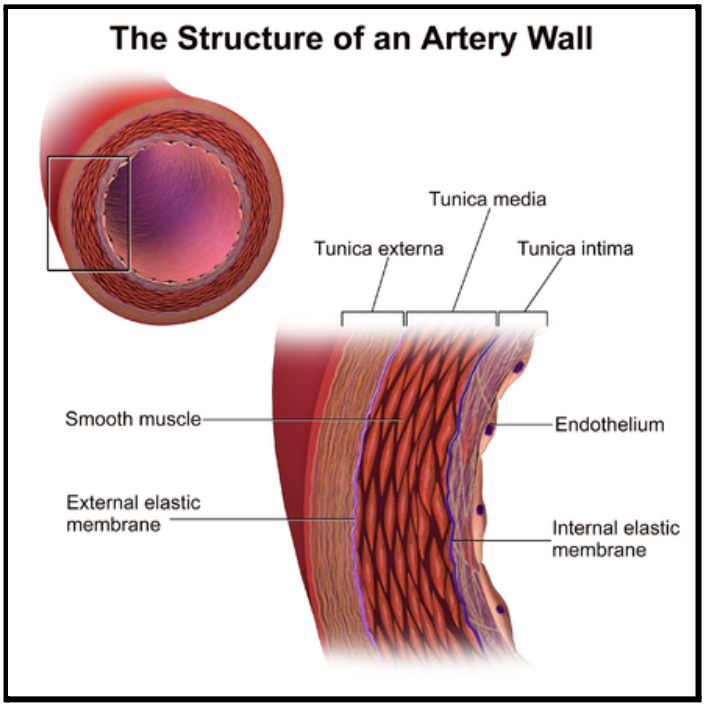
Blood Vessels

Blood is carried throughout the body by a vast network of blood vessels. The three main categories of blood vessels are arteries, veins, and capillaries. Arteries carry blood away from the heart, veins carry blood toward the heart, and capillaries are necessary for gas exchange at the level of the tissues. Two other types of blood vessels serve as connection points between the arteries and the capillaries, or arterioles, or between the capillaries and the veins, or venules. Blood travels through blood vessels depending on the pressure gradient and resistance of the blood vessel, which varies for each type depending on its cellular composition and function.[27]

Arteries

Arteries are the blood vessels that are the closest to the heart. They have relatively thick walls that consist of endothelial cells in the tunica intima, smooth muscle cells and elastic fibers in the tunica media, and collagen fibers in the tunica adventitia. The presence of these elastic fibers makes these vessels extremely elastic, meaning they can stretch and snap back into shape as necessary, and allows them to serve as a pressure reservoir. Their

elasticity also allows them to maintain blood flow through the whole system as they transport blood away from the heart. Arteries generally carry oxygenated blood, but there is one exception in that the pulmonary arteries carry deoxygenated blood from the right ventricle to the lungs to obtain oxygen.[30]



Wikipedia. *The Structure of an Artery Wall*.; 2014. https://en.wikipedia.org/wiki/Artery

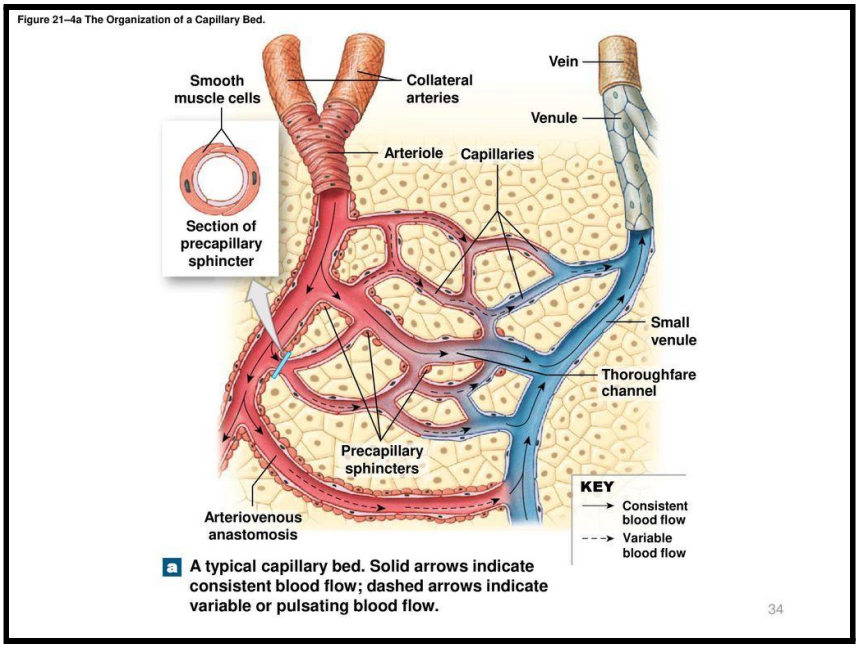
Arterioles

Arterioles connect arteries to the capillary beds. They are surrounded by smooth muscle which can decrease the radius of the vessels when the muscle contracts, and therefore increases the resistance, or hindrance to flow. The smooth muscle can also relax, increasing the radius and decreasing resistance. It is because of this structural quality that arterioles main function is to regulate blood flow to certain organs by increasing and decreasing resistance in certain areas. Unlike arteries, arterioles have very little elastic tissue and contain mostly smooth muscle that is innervated by the sympathetic nervous

system. The sympathetic nervous system can cause vasoconstriction to increase blood pressure or vasodilation to lower blood pressure when necessary.[30]

Capillaries

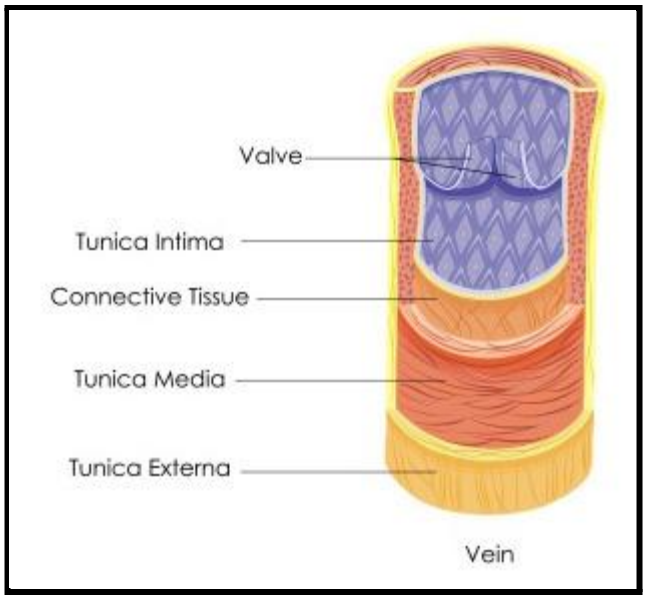
The main function of capillaries is to aid in gas exchange. While the individual radii of each vessel is relatively small, the presence of capillary beds allows for a massive cross sectional area, which keeps resistance in these vessels low by decreasing the speed at which blood travels through the capillary bed. The walls of capillaries are only one endothelial cell thick, and are different categories that serve different functions. Continuous capillaries can be found in skeletal muscle, lungs, and skin and make up a majority of the capillaries in the body. They are composed of solid endothelial cells with a solid basement membrane that only allows gasses and sugars to pass through. Fenestrated capillaries contain little windows in the endothelial cells that allow for gasses, sugars, and salts to pass through. These are found in the kidney. Sinusoidal capillaries, also known as discontinuous capillaries, have huge pores in both the endothelial cells and basement membrane that allow for gasses, salts, sugars, and even whole cells to pass through and are found in lymph nodes and the spleen.[30]



Fundamentals of Anatomy & Physiology. *The Organization of a Capillary Bed*.; 2018. https://slideplayer.com/slide/12165254/

Veins

Veins carry blood toward the heart from the rest of the body. They usually carry deoxygenated blood, but one exception to this rule can be found in the case of the pulmonary veins, which carry oxygenated blood from the lungs toward the left atrium. They serve as a blood reservoir and have a large radius, which allows for very little resistance to flow. They also have much thinner walls with less smooth muscle than arteries, which allows for them to be very compliant.[30] Compliancy is a very important characteristic of veins, because it means that they can distend in response to an increase in pressure.[9] Veins are not very elastic, because they contain more collagen fibers than elastin. One unique component of veins is that since they are moving blood against gravity, they contain one-way valves that prevent blood from pooling in our lower extremities. When the skeletal muscles surrounding veins contract, the veins are compressed and blood is pushed through the valve. Once the valve closes, blood is prevented from falling back down and it makes its way back to the heart in this fashion.[30]



Simbex. *Vein Structure*.; 2022. https://www.simbex.hr/en/health-of-feet-and-legs/human-blood-circulation/vein-structure/

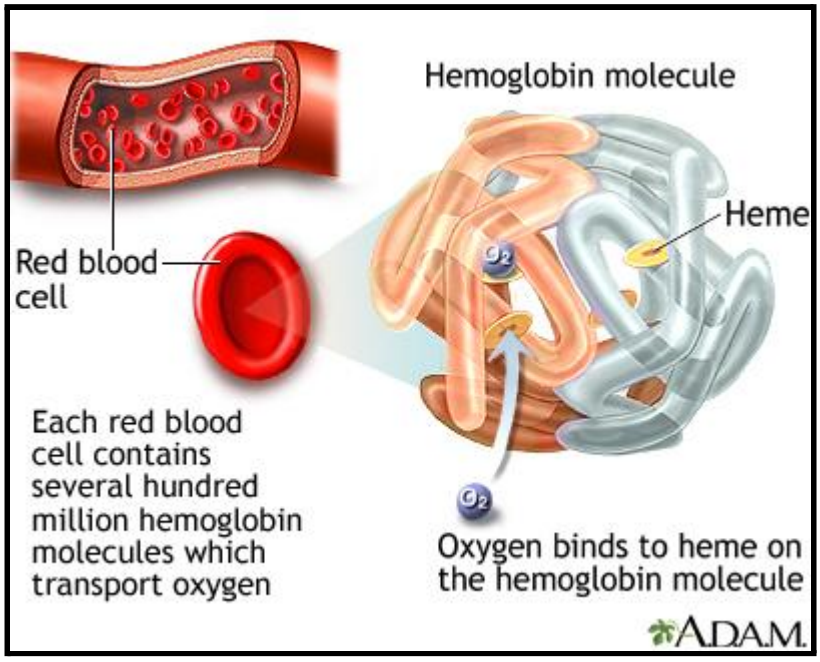
Blood

The blood is a vital part of the cardiovascular system and it represents around eight percent of our body weight. The average adult has about 5 liters of blood circulating through the vessels and the heart. Its main functions are to transport oxygen, nutrients, and hormones to the rest of the body, to remove waste from tissues, and to fight infection.[31] Arteries generally carry oxygenated blood to the body, and veins carry deoxygenated blood back to the heart. The one exception to this rule is in the pulmonary circulation, where the pulmonary arteries carry deoxygenated blood to the lungs to get oxygen, while the pulmonary veins carry oxygenated blood back to the heart.[30] The two different components of blood, both cellular and acellular, work together to ensure the tissues remain alive and healthy.

Cellular Components of Blood: Erythrocytes

There are three main types of cells that make up the cellular component of blood: erythrocytes, leukocytes, and thrombocytes. Erythrocytes, also known as red blood cells, are the most abundant cell type in blood. Their shape, a biconcave disc, maximizes their

surface area and allows them to perform their main function, carrying oxygen to tissues and carbon dioxide back to the lungs to be removed from the body.[32] They are thin and flexible, which helps them to squeeze through even the tiniest vessels, the capillaries, which are only wide enough for one red blood cell to pass through at a time.[30] Red blood cells contain a specialized molecule called hemoglobin, which is a polypeptide composed of 4 peptide chains that undergo a conformational change when bound to oxygen. Each hemoglobin can carry 4 oxygen molecules, with one in each peptide chain.[25]



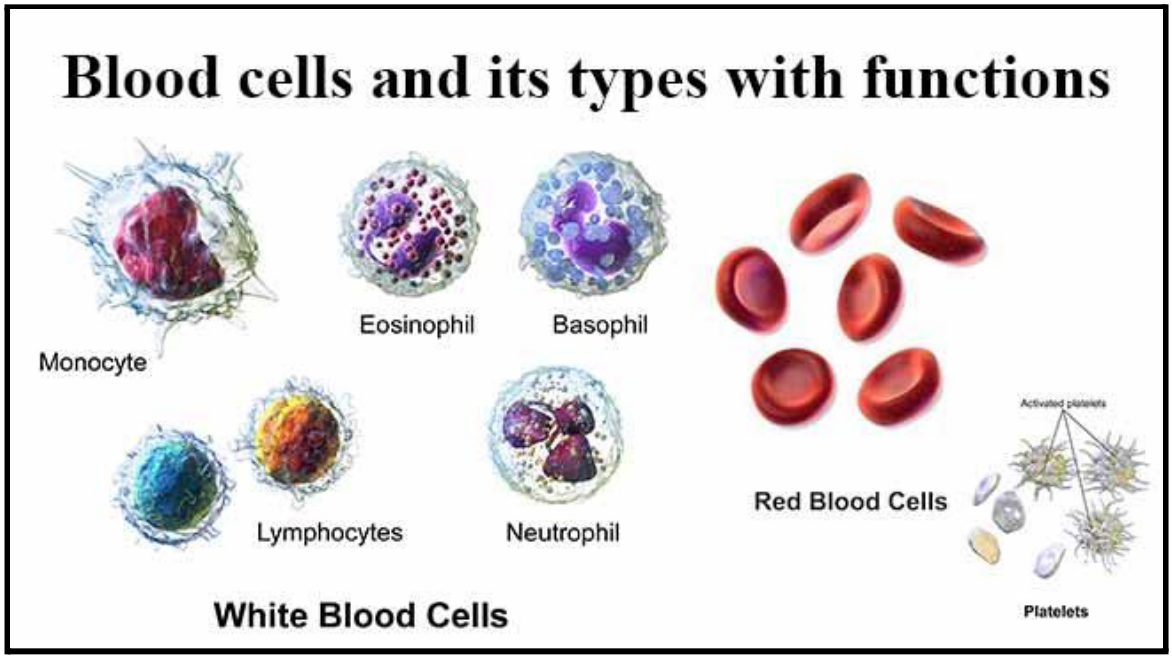
Penn Medicine. *Red Blood Cell and Hemoglobin*.; 2020. https://www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/anemia

Leukocytes

Leukocytes, also known as white blood cells, function to aid in the immune response and fight against infection.[33] They can be split into two categories: granulocytes and agranulocytes. Granulocytes include neutrophils, basophils, and eosinophils. Neutrophils are phagocytes, which means they assist in the immune response by cleaning up cellular debris and waste. They also play a very important role in inflammation and are

the first responders in the immune response. Basophils are the leukocytes that exist in the lowest number in the blood. They store and release histamine, which is involved in allergic reactions, and heparin, which is an anticoagulant. Eosinophils also contribute to allergic reactions and parasitic infections.[34]

Agranulocytes include monocytes and lymphocytes. Monocytes differentiate into macrophages, which consume debris and bacteria at the site of infection. There are two different types of lymphocytes, each with their own specialized functions. B Lymphocytes, or "B cells", secrete antibodies while T Lymphocytes, or "T cells", destroy or help other cells destroy target cells.[34]



Microbiology Info. *Blood Cells and Its Types with Functions*.; 2019. https://microbiologyinfo.com/blood-cells-types-functions/

Thrombocytes

The last cell type in the blood are thrombocytes, which are also known as platelets. Platelets are actually cell fragments that slough off of a larger cell, a megakaryocyte, in the bone marrow. They have a very short lifespan of only 8-10 days and are smaller than a red

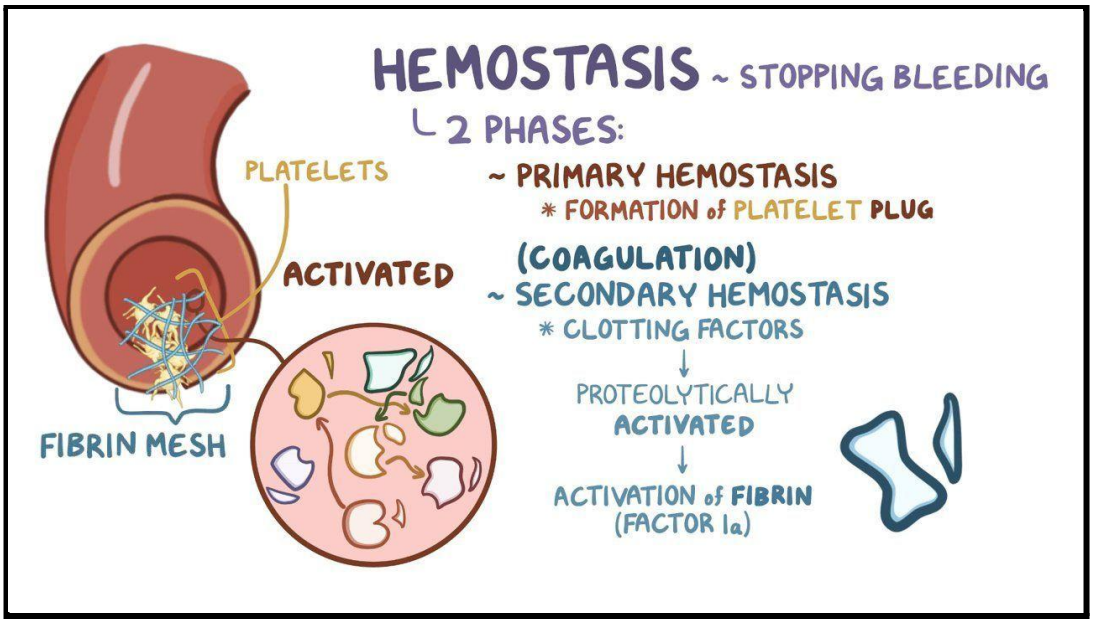
blood cell. Platelets function to aggregate and coagulate, which means they play a very important role in the wound healing process and clot formation.[36]

Acellular Component of Blood: Plasma

Plasma makes up a majority of the acellular component of blood. It consists of 90% water and is used as a transport medium for many substances, both inorganic and organic. The inorganic constituents of plasma make up only one percent of its volume, and include ions such as sodium, potassium, and calcium. The organic components make up around eight percent of plasma volume and consist of the plasma proteins: albumins, globulins, and fibrinogen.[36] Albumins bind and carry many substances that are insoluble in the blood such as certain hormones, drugs, and fatty acids. Globulins and fibrinogens are vital in the immune response and blood clotting.[10]

Blood Clotting and Dissolution

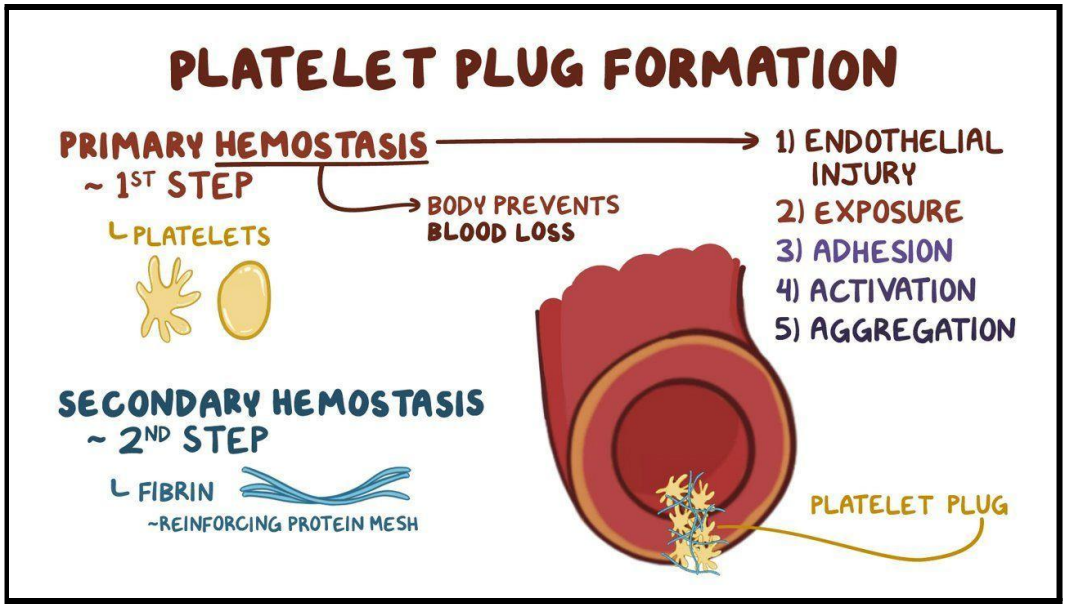
Blood clotting, also known as coagulation or hemostasis, both serves physiological purposes and is an indicator of pathological events.[5] In the physiological response to injury, platelets and plasma proteins come together in a process called the coagulation cascade.[13] This process is a delicate balance between clot formation, maintenance, and dissolution. When one part of the cascade fails to work, this could lead to hemorrhage, or excessive bleeding, or the blood clots that form and do not dissolve could dislodge and travel to the heart or brain, causing a heart attack or a stroke.[2] All of these instances are life-threatening conditions, and could be fatal if not treated immediately, which is why this process is so heavily regulated. There are two major steps to this process, the formation of a platelet plug, or primary hemostasis, and the coagulation cascade, or secondary hemostasis.[10]



Tarantino C. What is the coagulation cascade? Osmosis. Published 2022. Accessed April 27, 2022. https://www.osmosis.org/answers/coagulation-cascade

Primary Hemostasis

The first step in coagulation is primary hemostasis, which consists of the formation of a platelet plug in response to injury. If the endothelium, the innermost lining of the blood vessel, is damaged, a signal is sent that causes vasoconstriction, in order to slow blood loss from the vessel. The next step in this process is the exposure of collagen fibers within the vessel wall causing the release of Von Willebrand's factor, a protein that is released from endothelial cells and binds to the exposed collagen fibers. This leads to the third step, adhesion, where platelets bind to the Von Willebrand's factor using specialized proteins called GP1B, which are found on the surface of platelets. This binding leads to the fourth step, activation, where platelets change their shape in order to more easily bind with other platelets. Once bound, the platelets then release more Von Willebrand's factor and other substances to attract more platelets to the area, creating a positive feedback loop. The fifth and final step of primary hemostasis is aggregation, which completes the platelet plug formation at the injured area.[8]



Marshall T, Debevec-McKenney E, McBundy S, Watts S. Osmosis - A Better Way To Learn - Platelet plug formation (primary hemostasis): Video. Osmosis. Published January 21, 2022. Accessed April 27, 2022. https://www.osmosis.org/learn/Platelet_plug_formation_(primary_hemostasis)

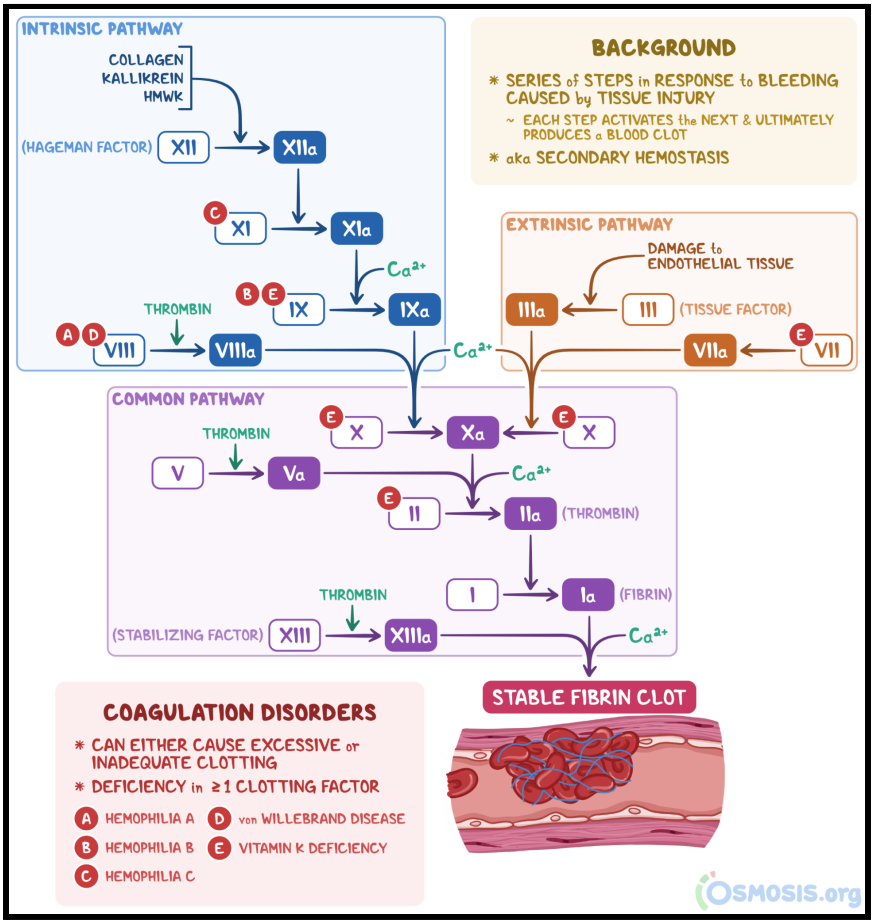
Secondary Hemostasis

The coagulation cascade is the name of the process that leads to the formation of a blood clot in response to two different stimuli: damage to cells outside of a blood vessel, which is mediated by the extrinsic pathway, and damage to collagen or other molecules that signal damage inside a blood vessel, which is mediated by the intrinsic pathway.[10]

The extrinsic pathway begins when an enzyme called factor VII binds to Tissue Factor and calcium, both of which are being released from the platelet plug that was formed in primary hemostasis. This leads to activated factor VII, which is now called factor VIIa, creating a complex with the Tissue Factor (TF) on the smooth muscle cell surface. This complex, VIIa-TF, cleaves and activates factor X into factor Xa, which in turn cleaves and activates factor V into factor Va. This is the start of the common pathway, which is shared by the extrinsic and intrinsic pathways of the coagulation cascade. Factor Xa uses factor Va and calcium to create the prothrombinase complex which activates factor II into factor IIa, also known as thrombin. Thrombin is an extremely important molecule in the

coagulation cascade, and it amplifies the effects of the pathway. It activates platelets, factor V and factor VII, which cleaves factor I into factor Ia, also known as fibrin. Fibrin creates long chains in the blood that act as a net to hold the platelet plug in place. This mesh created by fibrin is further strengthened when thrombin cleaves and activates factor XIIIa, which binds calcium and forms cross links between the chains.[13]

The intrinsic pathway begins when factor XII is activated by the platelet plug and becomes factor XIIa. This starts a chain reaction where factor XIIa cleaves and activates factor XI, which cleaves and activates factor IX. Factor IXa binds calcium and forms a complex with factor VIIIa to cleave and activate factor X. This feeds back into the common pathway, which ends with the formation of the fibrin mesh.[13]



Tarantino C. What is the coagulation cascade? Osmosis. Published 2022. Accessed April 27, 2022. https://www.osmosis.org/answers/coagulation-cascade

Dissolution

After the wound has healed and there is no fear of excessive bleeding from the injury site, blood clots should naturally begin to dissolve on their own.[6] This process, known as the fibrinolysis cascade, involves the activation of plasmin from plasminogen by many factors. Plasmin works to break down fibrin and destroy the mesh that is holding the blood clot together.[6] This process is as heavily regulated as the coagulation cascade, and needs to happen correctly in order to prevent clots from traveling throughout the body or occluding a blood vessel.

Types of Blood Clots

Blood clots can be categorized based on where they are formed in the cardiovascular system, arteries or veins, or where they are formed anatomically in the body.[4] Arterial clots are clots that form in an artery. Since arteries are usually transporting oxygenated blood to the rest of the body, a clot occluding an artery can lead to serious complications, as it prevents some area of the body from receiving oxygen and nutrients. Venous clots form in the veins. These clots form more slowly and their side effects become more noticeable over time.[4] Anatomically, clots form in the extremities, the heart, the lungs, the brain, or the abdomen. Each of these types of clots can cause a variety of symptoms, and can be life-threatening if not resolved quickly. A blood clot that is stationary in a vessel is called a thrombus, while a blood clot that breaks loose and travels to another site in the body is called an embolus.[1]

There are a few types of clots with special names based on where they are found in the body. The most common type of blood clot is called a deep vein thrombosis, or a DVT, which is a clot that has formed in a major vein anywhere in the body, but is most commonly found in the leg.[1] This can cause pain around the site of the clot and even slight discoloration in the skin. DVTs

should be taken care of immediately because, in some cases, they can dislodge and lead to a pulmonary embolism, which is a clot that has traveled to the lung.[6] Depending on where the clot is in the lung, this condition can be fatal, as it cuts off blood supply to the lung and prevents oxygenated blood from returning to the heart. Side effects of a pulmonary embolism include extreme pain in the chest and side and difficulty breathing. When left untreated, a PE could lead to a pulmonary infarction, which is when a section of lung tissue dies due to lack of oxygen.[12]

Risk Factors

There are certain factors that put the average person at a higher risk for developing blood clots. Some lifestyle risk factors include smoking, obesity, and poor dietary habits. All of these put unnecessary stress on the cardiovascular system and make it more difficult for clots to naturally dissolve if they do form.[5] Pregnancy is also a risk factor for developing blood clots due to the increase in blood volume necessary to provide nutrients and oxygen to the developing fetus. This leads to an increase in platelets and clotting factors, which increases likelihood of developing a blood clot.[14] Prolonged bed rest or sitting for long periods of time also increase the risk of a blood clot, which is why it is important to walk and stretch when on long plane or car rides to keep blood pumping.[14]

Diseases and Conditions

There are many diseases and conditions that increase the risk of developing a blood clot. One example is atherosclerosis, which is an increase in plaque buildup in the arteries. If plaque breaks off, platelets will respond to this site as if it is a normal blood vessel injury, and form a blood clot.[14] The plaque buildup also makes the opening of the blood vessel smaller than normal, which makes it difficult for blood to flow through the vessel, causing turbulence. Turbulent blood flow occurs when blood flows through the vessel in a

disorderly fashion, which causes it to bump against the vessel wall and form currents, increasing the risk of clot formation.[7] Diabetic individuals are also at an increased risk of developing blood clots, due to increased plaque buildup in the arteries, as well.[14]

Atrial fibrillation, also known as A-fib, is a type of irregular heartbeat, which is called an arrhythmia. This occurs when the upper chambers of the heart, the atria, beat out of sync, and much faster than the lower chambers of the heart, the ventricles. This condition may be asymptomatic, or can cause shortness of breath, chest pain, and dizziness. In atrial fibrillation episodes, heart rate can reach as high as 175 beats per minute, where the normal range is anywhere from 60 to 100 beats per minute. The disordered heartbeat causes the upper chambers of the heart to not empty properly, and blood can start to collect in the atria. This blood can form a clot that could break off and travel to the brain and cause a stroke.[15] Patients with A-fib are often put on blood thinners (anti-coagulants) for life, along with other treatment methods for the condition itself to prevent this dangerous complication of the disease.[5]

Medications

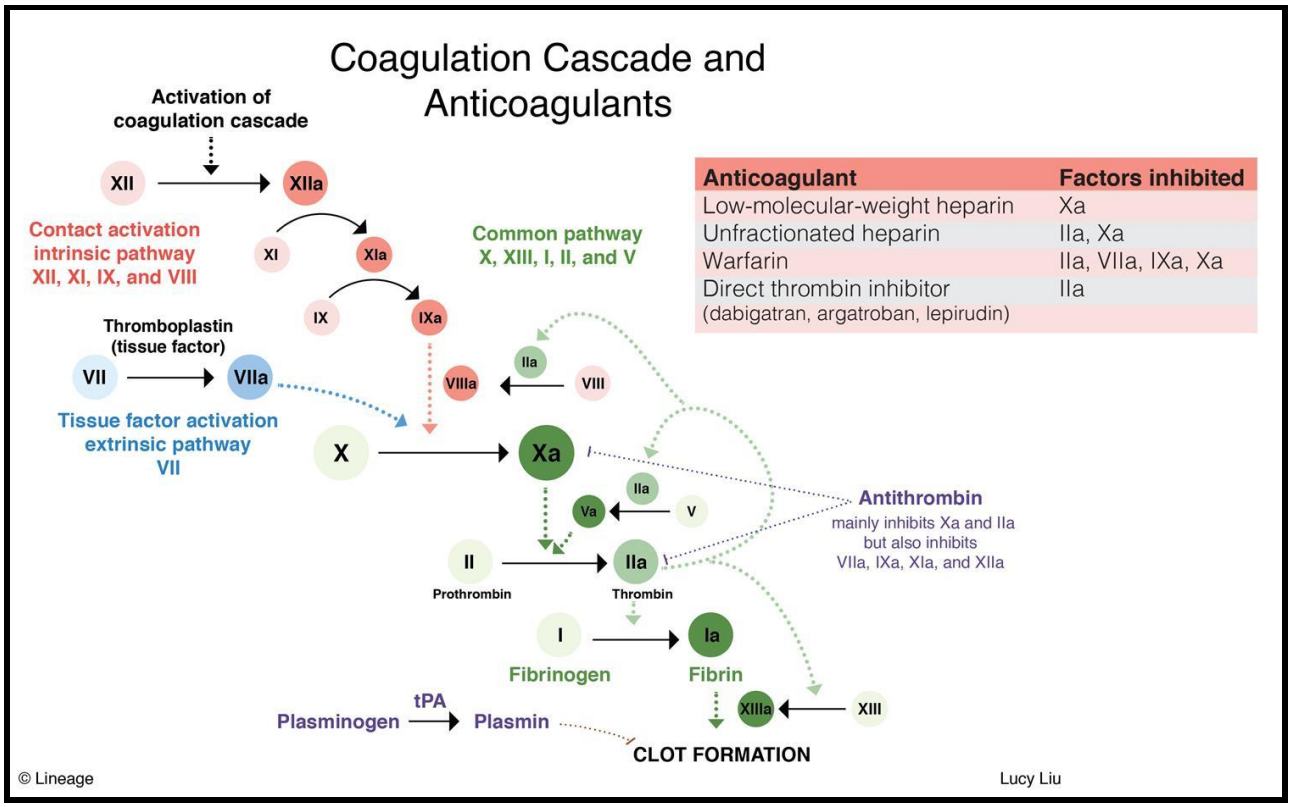
Certain types of pain medications called nonsteroidal anti-inflammatory drugs, or NSAIDs, can increase the risk of developing cardiovascular issues including blood clots and heart disease. This risk increases with prolonged use and high doses of these medications, but still exists for the average user. NSAIDs increase the risk of developing a blood clot by reducing the production of enzymes that work to inhibit clots, which causes an imbalance and increases the likelihood of clot formation.[11]

Hormonal birth control methods, such as the pill, IUDs, and implants, can also increase risk of developing blood clots. Around 1 in 3,000 women who use hormonal birth

control methods will develop a blood clot in a year.[15] This risk is most prevalent in women who have a method that uses a combination of both estrogen and progesterone. Estrogen is the main risk factor in these treatment methods, as it increases the levels of clotting factors in the blood. On the other hand, progesterone, or the synthetic form progestin, does not significantly increase the risk of developing blood clots. However, for patients with a personal medical history of clotting or a family history of blood clotting disorders, the safest option is to use non-hormonal birth control methods.[15]

Treatment and Prevention

The treatment of blood clots depends on the location and severity of the clot. They are usually diagnosed using a CT scan of the affected area, and may be followed up with other tests such as an echocardiogram or chest X-ray to determine the severity of the damage caused by the clot and how it has affected other parts of the body.[1] Once located, if the clot does not seem to be likely to dislodge and travel to the rest of the body, or if it not completely occluding any major vessels, they can usually be treated with IV anticoagulants, such as Tissue Plasminogen Activator (tPA), in the hospital and subsequent tablets to be taken over a period of 6 months to a year.[5] Anticoagulants work to prevent other blood clots from forming and give the body time to resolve the clots on its own.[6] If, however, the clot is in a high risk area or could travel and cause a heart attack or stroke, surgery may be required to remove the clot from the vessel.[5]



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Since there are many different factors that could increase risk of developing blood clots, it is important to weigh the benefits and risks of each treatment method for other conditions. Overall, the best ways to prevent blood clot development is by maintaining a healthy lifestyle with exercise and a balanced diet to promote good cardiovascular health and seek immediate medical attention if you notice any signs and symptoms that could indicate a blood clot.[5]

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