Overview of the Cardiovascular System and the Blood 5.1

Learning Objectives

- Calculate the time of diffusion as a function of distance
- Describe the components of the cardiovascular system and their function
- List the classes of important materials carried by the blood
- Describe the location and function of the interstitial fluid
- Identify the major arteries and veins from their anatomic location
- Distinguish between the systemic and pulmonary circulation
- Describe what is meant by a portal circulation
- Explain why the output of the heart is almost always exactly equal to its input
- Define vascular resistance
- Define vascular compliance
- Define the hematocrit
- Describe hemostasis in general terms
- Describe the role of platelets in blood clotting
- Distinguish between the intrinsic and extrinsic pathway in blood clotting
- Describe the chemical reaction that directly forms a clot
- Describe the function of plasmin and how it is activated

THE CIRCULATORY SYSTEM IS A TRANSPORT SYSTEM

The central organizational theme of large, multicellular creatures such as ourselves is that the cells, in general, are not directly connected to the external environment. They are directly connected to the internal environment, which is the interstitial fluid, and indirectly connected to the environment through a medium of exchange, and that medium is the blood. The blood allows cells to have indirect contact with the external environment through the filters of the lungs, intestines, kidneys, and the skin. The internal environment that bathes the cells must be supplied with nutrients for the cells, must have waste products removed, and must have the heat that the cells generate dissipated to the external environment. This overall organization is shown schematically in Figure 5.1.1

THE CIRCULATORY SYSTEM CONSISTS OF THE *HEART*, *BLOOD VESSELS*, AND *BLOOD*

Figure 5.1.1 shows the three main components of the circulatory system: the heart, the blood vessels, and the blood. Each performs an irreducible function that cannot be provided by the other components.

The **heart** is a bag of muscle that encloses a part of the blood and that contracts rhythmically to move blood from the veins, at low pressure, to the arteries at high pressure. It is actually four bags of muscles (see Figure 5.1.1) arranged in series, but their contraction is nearly simultaneous. The heart has valves that make flow unidirectional. The heart contracts about once a second (70 beats per minute) and has its own rhythm generator, the pacemaker. Specialized excitable cells form an electrical system that coordinates the heart beat between its four chambers.

The blood vessels are hollow tubes that are conduits for the blood. They are collectively called the **vascular system**. The blood vessels are of five major types: **large arteries**, **arterioles**, **capillaries**, **venules**, and **major veins**. **Arteries always carry blood away from the heart** and withstand high pressures.

Arterioles are smaller versions of the arteries that are important in the regulation of blood flow. The capillaries are tiny tubes that are often about the same size as the red blood cells. They allow close but indirect contact of the blood with the tissues. Here, water, gas, and solute exchange between the blood and the tissues. **The venules and veins carry blood toward the heart** and generally have a low pressure.

The vascular system has four main functions:

1. Transform pulsatile flow from the heart beat into more continuous flow.
2. Distribute the blood to various organs.
3. Exchange materials in the tissues.
4. Veins serve as a volume reservoir.

THE CIRCULATORY SYSTEM CARRIES NUTRIENTS, WASTES, CHEMICAL SIGNALS, AND HEAT

The whole point of the circulatory system is to carry something in the blood. Blood contains a variety of

DOI: http://dx.doi.org/10.1016/B978-0-12-800883-6.00044-6

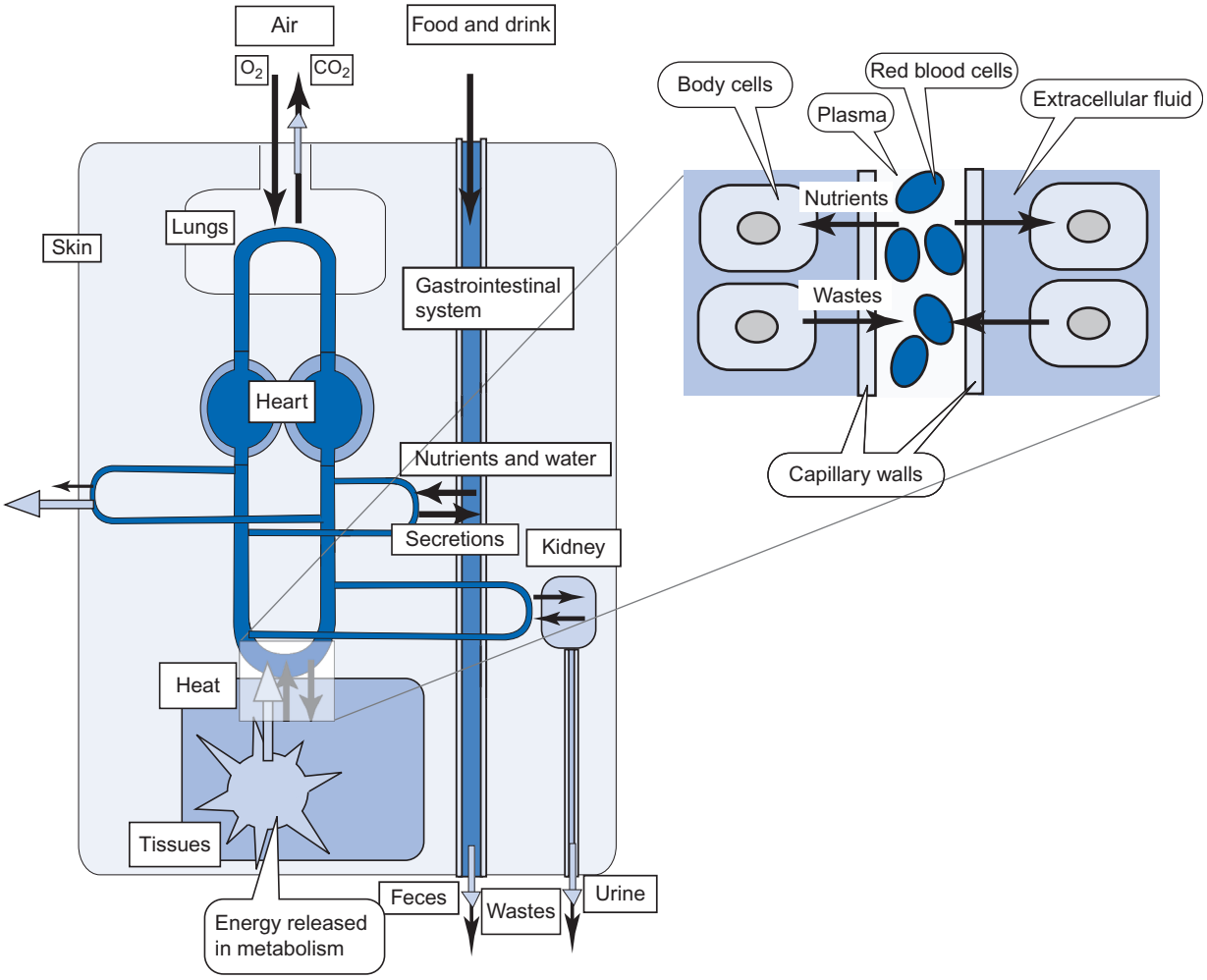


FIGURE 5.1.1 Overall plan of the circulatory system. Cells require supply of nutrients and removal of waste material and heat. Because they are far from body surfaces, nutrients are delivered and wastes removed through the medium of the blood, contained within vessels, and moved through the system by pressure generated by the beating heart. The final purpose of the cardiovascular system is to transport materials to the tissues (inset) where materials can exchange into the **interstitial fluid** that immediate surrounds the cells. Black arrows indicate mass exchange; light arrows indicate energy exchange.

materials, including water, salts, dissolved proteins, nutrients, and a variety of different cell types. Table 5.1.1 contains a partial listing of the huge variety of materials carried by the blood. These come under four main categories: nutrients, wastes, chemical signals, and thermal energy. Although not commonly thought of as a nutrient, the primary material being transported to the cells is oxygen. Because it occupies a central place in metabolism, oxygen levels in the tissues is homeostatically regulated. Many of these items are transported from a **source** to a **sink**. In addition, the blood contains a large variety of things that are being carried for the purpose of being part of the blood. These include the plasma proteins and the formed elements of the blood, the red and white blood cells.

THE CIRCULATION IS NECESSARY BECAUSE DIFFUSION FROM AND TO THE ENVIRONMENT IS TOO SLOW

Single-celled, free-living organisms do not have closed circulatory systems because they are small enough that simple diffusion between the cell and the outside environment adequately exchanges gases such as oxygen and carbon dioxide and nutrients such as glucose and amino acids. The time of one-dimensional diffusion is related to the diffusion distance according to

$$\bar{x}^2 = 2D\,\Delta\, t \qquad [5.1.1]$$

where $\bar{x}^2$ is the average square displacement from $x = 0$, the starting point of diffusion, D is the diffusion coefficient, and Δt is the elapsed time. Consider the diffusion of oxygen, with a diffusion coefficient of 1.8×10^{-5} cm^2 s^{-1}. Table 5.1.2 shows that diffusion is extremely rapid over short distances, 0–1 μm. At cellular distances, oxygen diffusion is also rapid, requiring a few seconds to travel 50 μm. Over longer distances, diffusion becomes quite slow. As organisms increased in size, they encountered diffusion limitations. The solution to increase delivery of materials in large, multicellular animals is to increase the flow of materials by **convection**. The one-dimensional convection–diffusion equation was given earlier as Eqn [1.6.36]:

TABLE 5.1.1 Partial Listing of Materials Carried in the Blood

Nutrients	Waste Products	Chemical Signals	Thermal Energy
Water	CO_2	Growth hormone	Metabolic heat
Oxygen	Urea	ACTH, LH, FSH	
Glucose	Ammonia	Prolactin, TSH	
Amino acids	Uric acid	ADH, oxytocin	
Fatty acids	Creatinine	Thyroxine	
Vitamins	Lactic acid	PTH	
Lipids as lipoproteins	Acetone	Insulin, glucagon	
Na, K, Ca, Mg	Acetoacetic acid	Epinephrine	
Fe, Zn, Cu, Mn	β-hydroxybutryic acid	Erythropoietin	
Cl, I, PO_4, SO_4	Enzymes: SGOT, LDH	GI hormones	
		Gastrin, CCK	
		Motilin, secretin	
		Somatostatin	

TABLE 5.1.2 The Calculated Time for One-Dimensional Diffusion for O_2 in Water for Various Distances

Physiological Distance	Distance	Time for O_2 Diffusion
Cell membrane	10 nm	28×10^{-9} s
Mitochondrion	1 μm	0.28×10^{-3} s
Nucleus	10 μm	28×10^{-3} s
Large muscle cell	100 μm	2.8 s
Small muscle length	1 cm	7.8 h
Larger muscle	10 cm	32 days

Note that diffusion is extremely fast over short distances but is very slow for longer distances.

$$[5.1.2] \qquad J_s = -D\frac{\partial C(x,t)}{\partial x} + J_v C(x,t)$$

Convection, the movement of materials by flow, adds the term, J_vC, to the diffusional flux. This convectional term is the part of the flux or transport of solute that occurs when solute is carried along by the bulk flux of fluid. This one-dimensional equation is a simplification of the equation that considers the flux as a three-dimensional vector. In three dimensions, the spatial partial derivative of $C(x, t)$ in Eqn [5.1.2] is replaced with the **gradient** of C, a vector, and J_v is the velocity of fluid that carries the solute, which is also a vector. The resulting flux of solute is also a vector that gives the magnitude of the flux and its direction. In large animals the convection term dominates the total flux, because the distances are large and the gradients of C are small.

THE CIRCULATORY SYSTEM CONSISTS OF THE *PULMONARY CIRCULATION* AND *SYSTEMIC CIRCULATION*

The anatomic arrangement of the major blood vessels is shown in Figure 5.1.2. Only the major vessels are shown because otherwise the entire diagram would be occupied by vessels. Every cell of the body is within a few hundred microns of a vessel.

The heart is actually a dual pump. The right heart pumps blood into the **pulmonary artery** to the lungs where blood is replenished with oxygen and waste CO_2 is removed. The blood collects in the **pulmonary veins** and returns to the heart. The flow of blood from the right heart to the lungs and back to the left heart is called the **pulmonary circulation**. The pulmonary

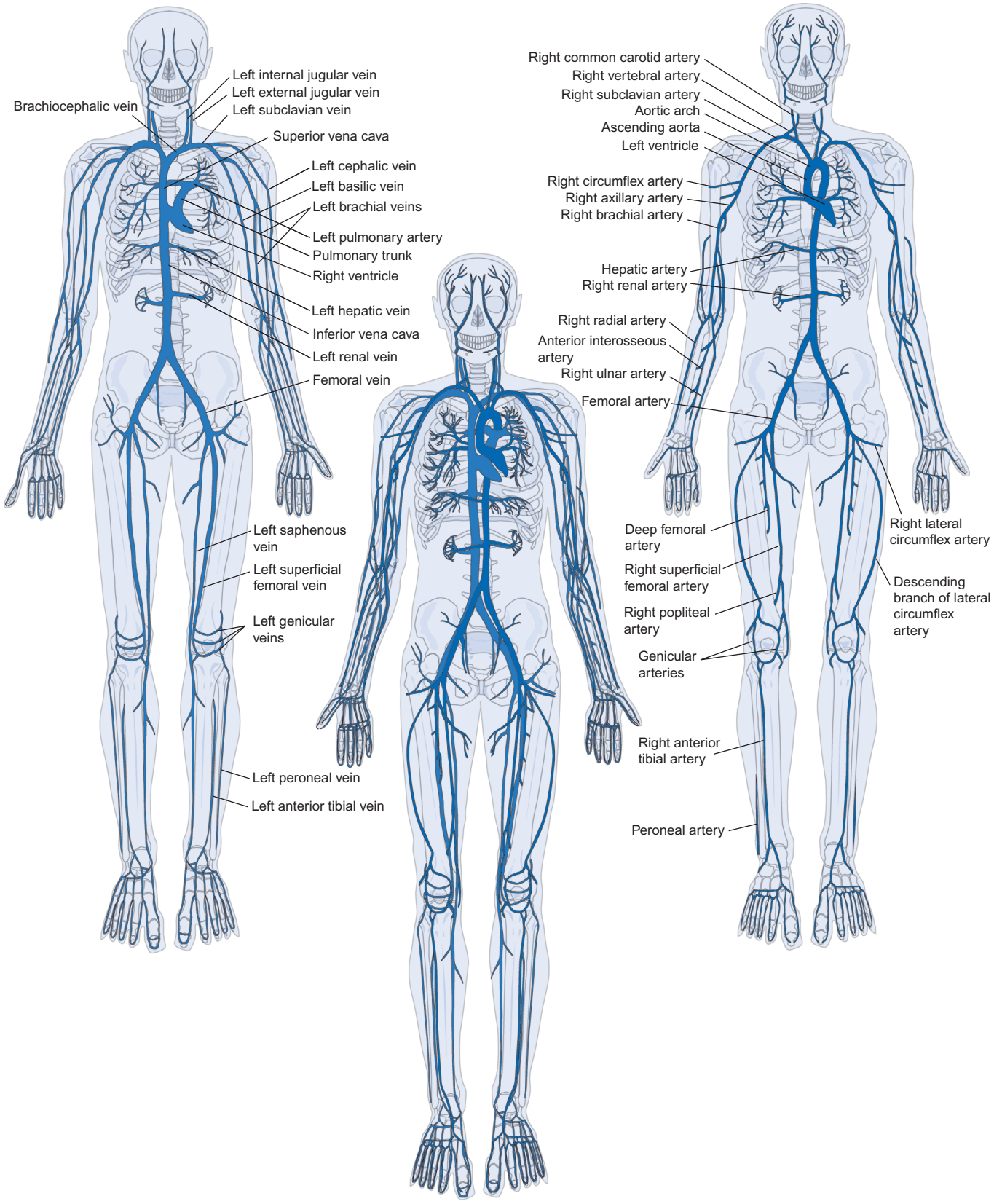


FIGURE 5.1.2 Simplified anatomy of the cardiovascular system. The venous system is shown on the left, in light blue. The arterial system is shown on the right, in darker blue. The combined circulatory system is shown in the middle. Only the major arteries and veins are shown and the vessels supplying the intestines have been omitted for clarity. Vessels have been labeled for only one side of the body. As can be seen, the veins and arteries typically are paired so that every artery has an associated vein.

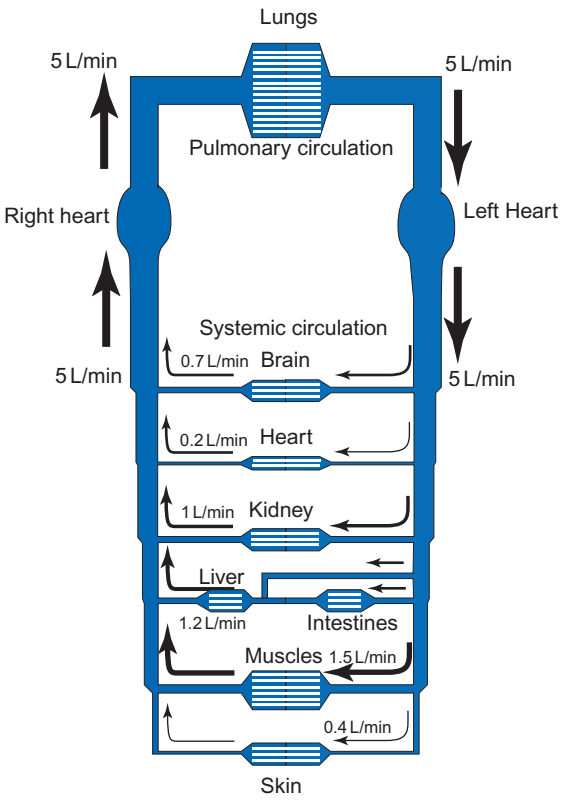


FIGURE 5.1.3 General layout of the circulation and typical flows at rest. The pulmonary circulation is in series with the systemic circulation, and therefore the flow through the pulmonary circulation is equal to the flow through the systemic circulation.

circulation is in series with the **systemic circulation**, the circulation from the left heart into the aorta and then to the rest of the body. Although the dual pump is in series, the pumping is simultaneous, not sequential. The vessels of the systemic circulation are generally arranged in parallel. This arrangement allows for independent regulation of blood flow to the various organs.

Because the circulatory system is closed, the flow at steady state into the right heart must be equal to the flow out of the right heart, which must be equal to the flow into the left heart and the flow out of the left heart. Because the vessels are slightly elastic, temporary differences in the output of the right heart and left heart cause shifts of fluid from the venous to the arterial side or vice versa.

MOST CIRCULATORY BEDS ARE ARRANGED IN *PARALLEL*

Most of the major arteries supplying the organs are arranged in parallel, as shown in Figure 5.1.3. The flow of blood encounters a hydrodynamic resistance in the vessels that perfuse each organ. By adjusting the resistance (by vasodilation or vasoconstriction), flow through each organ can be regulated more or less independently from the flow through other organs.

There are some exceptions to the parallel arrangement of flow. In the gastrointestinal tract, blood first perfuses the intestine and then perfuses the liver in the portal circulation. In this case, blood travels through two capillary circulations in series. A second example occurs in the kidneys. The first set of capillaries is a high-pressure circulation that forms the glomerular filtrate (see Chapter 6.2) as the first step in making urine. Blood that drains from these capillaries then flows through the efferent arteriole and then breaks up into a second set of capillaries, the peritubular capillaries.

PRESSURE DRIVES BLOOD FLOW THROUGH THE VASCULAR SYSTEM

Newtonian mechanics tells us that materials at rest remain at rest unless acted upon by an outside force and that materials in motion remain in motion unless acted upon by an outside force. After the heart accelerates a volume of blood, its energy would be gradually dissipated by distension of the arterial walls and friction with the walls of the vessels and within the fluid itself, unless a second heart beat, and then a third and fourth, continually provided force to keep the fluid moving. To maintain a flow through a resistance, there must be a continuous application of a force. When this force is normalized to the area over which it operates, it is the pressure. The first law of the cardiovascular system is written as:

$$Q = \frac{\Delta P}{R} \quad [5.1.3]$$

where Q is the flow (in units of volume per unit time), ΔP is the pressure difference separated by the distance along which flow occurs, and R is the resistance of the tube through which flow occurs. This is a hydrodynamic analogue of Ohm's law for the flow of current. This law is valid only for laminar flow.

Laminar flow is streamlined flow that occurs, for example, when water is gently poured from a pitcher. Laminar flow through rigid, straight tubes can be described by Poiseuille's law (Eqn [1.2.17]), which has a steep dependence on the caliber of the tube. Poiseuille's law applies only to long, straight tubes under conditions of laminar flow. It is not valid in a network as complicated and varying as the cardiovascular system. Turbulent flow is chaotic, like the flow of a river around an obstacle at flood stage: the velocity of water flow at different points in the stream can point almost anywhere, including back upstream.

Despite the limitations to application of Poiseuille's law to the vasculature, resistance of the vessels can increase by vasoconstriction and decrease by vasodilation. The rules of addition of resistances in series and parallel are exactly analogous to those in electrical circuits.

VESSELS ARE CHARACTERIZED BY A *COMPLIANCE*

The cardiovascular system is a closed system, but it is ***elastic***. What this means is that it does not have a defined volume. The volume can increase or decrease

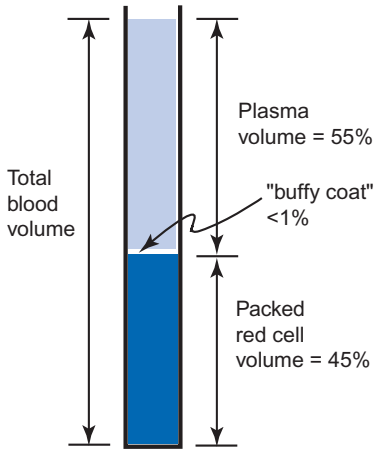


FIGURE 5.1.4 Whole blood after centrifugation in a cylindrical tube. The blood separates into a fluid phase, the plasma, that contains electrolytes, proteins and lipoproteins, and a packed cell layer containing primarily erythrocytes. At the interface between the plasma and the packed red cells is a "buffy coat" of white blood cells and platelets. The **hematocrit ratio** is the ratio of the packed cell volume to the total volume. The hematocrit is the hematocrit ratio × 100. Normal values for the hematocrit are 42–52% for men and 37–47% for women.

and the system responds by expanding or shrinking. The insertion of extra volume and the accompanying expansion of the vessels is accompanied by a change in pressure. The relationship between a volume change and a pressure change is

$$[5.1.4] \qquad \Delta P = \frac{\Delta V}{C}$$

where ΔP is the pressure change, ΔV is the volume change, and C is the **compliance**. The meaning of compliance here corresponds to its nontechnical usage: a compliant system is one that expands easily. In the case of a very compliant system, an expansion by ΔV produces little pressure change. Rigid or noncompliant vessels do not expand easily and expansion by a small ΔV produces a large pressure change.

BLOOD CONSISTS OF CELLS SUSPENDED IN PLASMA

Blood makes up about 6–8% of the body mass by weight. Its density ranges from 1.05 to 1.06 g cm^{-3} and its viscosity ranges from 2.5×10^{-3} to 3.9×10^{-3} Pa s, about 3.5–5.5 times that of water. Blood is a non-Newtonian fluid, meaning that its viscosity is not independent of the applied shear rate (dv/dr, the gradient of velocity with radius, in units of s^{-1}), or of the diameter of the tube. The blood consists of two main components: **plasma** and **red blood cells**. The **white blood cells** make up a third, much smaller, component. Centrifugation of *unclotted* blood results in the separation of the cells from the plasma as shown in Figure 5.1.4. The plasma is a straw-colored fluid that contains electrolytes, proteins, metabolites, hormones, nutrients, and wastes.

Besides carrying innumerable materials, the plasma also defines the electrolytic composition and the osmolarity of the extracellular fluid and contains proteins that form and dissolve blood **clots**. The red blood cells carry primarily oxygen, but also buffer blood pH. The white blood cells are responsible for inflammation and the response to invasion by parasites and microbes.

HEMOSTASIS DEFENDS THE INTEGRITY OF THE VASCULAR VOLUME

Hemostasis is the arrest of bleeding when blood vessel integrity is breached. The complete healing of an injury to a vessel includes:

- vasoconstriction of the vessel;
- formation of a platelet plug;
- coagulation of the blood;
- clot retraction;
- clot dissolution;
- formation of connective tissue throughout the wound to form a permanent seal.

VASOCONSTRICTION AND BACK PRESSURE REDUCES BLEEDING

Disruption of a blood vessel allows blood to escape either to the outside of the body or into the extravascular space. Bleeding into the extravascular space builds up pressure in the tissue that partly restrains further bleeding. How fast the back pressure builds up depends on the compliance of the tissues. Surface wounds shed blood out of the body and no back pressure develops. Bleeding in this case is limited by vasoconstriction. Damaged vascular cells contract reflexly by a local myogenic mechanism elicited by vascular damage. Platelets release **thromboxane A_2 (TXA_2)** and **serotonin,** both potent vasoconstrictors. **Thrombin**, a protein that is activated during the coagulation cascade, elicits TXA_2 and serotonin release from platelets.

THE PLATELET PLUG CAN SEAL SMALL VASCULAR HOLES

Injury to blood vessels exposes collagen that binds platelets, causing them to **degranulate**, releasing adenosine diphosphate (ADP), TXA_2, serotonin, and lipoproteins. ADP and TXA_2 recruit platelets from the blood. Lipoproteins help initiate coagulation. Aggregation of platelets is accompanied by activation of myosin light chain kinase within the platelets, activating cytoskeletal elements to change the shape of the platelets. Aggregation of the platelets at the site of injury forms a plug that can seal small vessels temporarily.

BLOOD COAGULATION SEALS THE LEAK

Blood plasma contains **fibrinogen**, a large molecular weight (330 kDa), soluble protein. Conversion of fibrinogen into insoluble fibrin, and then cross-linking the fibrin, produces a tangled meshwork of filaments that comprises the blood clot. Plasma itself can clot, because it possesses fibrinogen. Serum is the fluid left after plasma has clotted, and so it can no longer clot. The clot is called a **thrombus**. If it contains only platelets, it

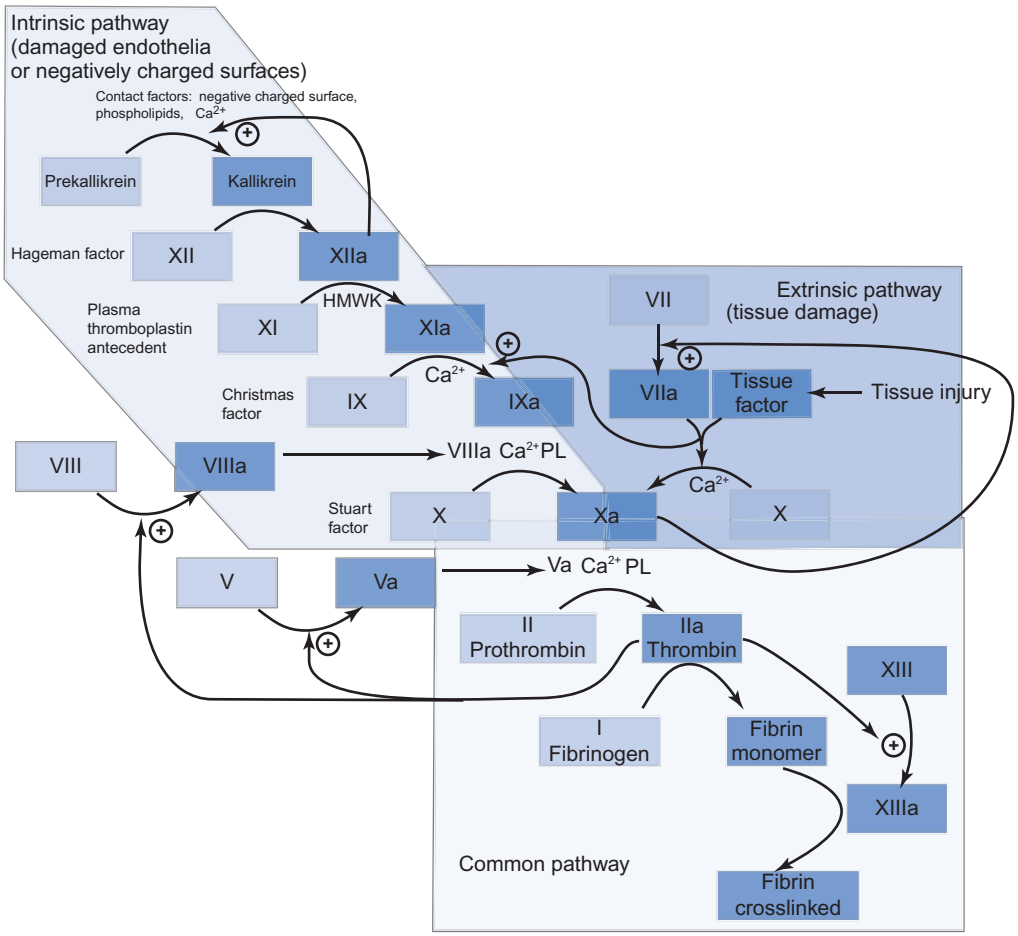


FIGURE 5.1.5 Summary of the clotting cascade. Roman numerals denote zymogen forms of the clotting factors. These inactive forms are enclosed in light blue boxes. The activated, proteolytic forms of the clotting factors are denoted by the suffix "a" and are enclosed in dark blue boxes. Blood typically clots *in vivo* by activation of the extrinsic pathway. Tissue factor, also called tissue thromboplastin, is a nonenzymatic lipoprotein expressed on the surface of cells that normally are not in contact with the blood. Tissue damage exposes blood to tissue factor, which binds factor VIIa and together they activate factor X to Xa. Factor Xa converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, which is the key step in clot formation. The clot is polymerized by factor XIIIa to form the dense network of fibrin strands. Although factor VII is activated to VIIa by the latter's product, factor Xa, it appears that blood contains trace amounts of VIIa sufficient to begin the clotting cascade. Blood coagulation by the intrinsic pathway occurs when blood is exposed to a negatively charged surface. HMWK stands for high-molecular-weight kininogen. Factors V, VIII, tissue factor, and HMWK are all nonenzymatic protein cofactors that increase the proteolytic activity of thrombin and factors Xa, VIIa, and XIIa, respectively.

is a **white thrombus**; a **red thrombus** entraps red blood cells as well. The formation of the clot and its cross-linking are controlled by **thrombin**, an enzyme formed from its plasma precursor, **prothrombin**. Activation of prothrombin to thrombin is the culmination of a series of events, shown diagrammatically in Figure 5.1.5.

CLOT RETRACTION DRAWS THE EDGES OF THE WOUND TOGETHER

During the first few hours after a clot forms, it retracts and extrudes serum. Clot retraction draws the wound surfaces together and also reopens any vessels that may be occluded by the clot. Close apposition of the wound surfaces enhances wound healing. Retraction is caused by the platelets.

PLASMIN DISSOLVES CLOTS

Endothelial cells release inactive **tissue plasminogen activator (tPA)** following injury. Fibrin activates tPA, which in turn activates plasmin by proteolytic cleavage of an inactive β globulin, **plasminogen**. Plasminogen binds to both fibrin and fibrinogen, so it is incorporated into the clot. Plasmin then proteolyzes fibrin. This mechanism accounts for most of the **fibrinolysis**, but other activators of the conversion of plasminogen to plasmin are present in plasma and urine (**urokinase**). Circulating baseline levels of plasmin are inhibited by α2-antiplasmin. tPA is also inhibited by specific inhibitors called **plasminogen activator inhibitor.** Four distinct inhibitors have been identified; PAI-1 and PAI-2 seem to be most important.

BLOOD COAGULATION SITS ON A KNIFE EDGE OF ACTIVATION AND INHIBITION

Coagulation normally occurs only when there is trauma to the blood vessels. What stops the clot from progressing throughout the entire vasculature? The answer is

that the blood contains a number of anticoagulants whose job is to prevent the clotting mechanism from getting out of hand. These are:

- thrombin inhibitors;
- antithromboplastin, also called tissue factor pathway inhibitor;
- heparin.

THERE ARE FOUR DISTINCT THROMBIN INHIBITORS

The thrombin inhibitors include **antithrombin III**, **α_2 macroglobulin**, **heparin cofactor II**, and **α_1-antitrypsin**. All of these are serine protease inhibitors. Antithrombin III is the most important because it inhibits the activities of thrombin and factors IXa, Xa, XIa, and XIIa. Antithrombin activity is stimulated by binding of **heparin**, a sulfated polysaccharide that is produced by basophils and mast cells and is present on the surfaces of endothelial cells. Heparin increases the activity of antithrombin III some 100- to 1000-fold, effectively preventing clot formation. The inhibition of factors IXa, Xa, XIa, and XIIa effectively stops the intrinsic pathway of blood coagulation.

ANTITHROMBOPLASTIN STOPS THE EXTRINSIC PATHWAY

Tissue factor pathway inhibitor (TFPI) is a 34 kDa protein that is found in plasma lipoproteins and bound to the vascular endothelium. It binds to and inhibits factor Xa. The complex Xa-TFPI then interacts with the complex of tissue factor VIIa and inhibits its activation of factors X and IX.

Clinical Applications: Bleeding Disorders

Hemophilia refers to the inability to clot blood. As you can see from Figure 5.1.5, there are a number of proteins involved in clotting and dysfunction of any of them could, in principle, lead to problems in clotting. Hemophilia A is the classical hemophilia due to an X-linked disorder that causes a deficiency in factor VIII. Factor VIIIa has no enzymatic activity in itself; it is a cofactor that increases the activity of IXa to convert factor X to Xa. To date, some 150 different point mutations in the factor VIIIa gene have been identified. Hemophilia A occurs in from 1:5000 to 1:10,000 males in all populations. Persons with factor VIIIa deficiency suffer from joint and muscle hemorrhage, easy bruising, and prolonged bleeding. The severity depends on the level of factor VIII activity. Treatment involves infusion with factor VIII isolated from human plasma or prepared by recombinant DNA technology.

Hemophilia B results from a deficiency in factor IX. Its prevalence is about 1/10th that of hemophilia A and, as with hemophilia A, the severity ranges from mild to severe depending on the factor IX activity in plasma. Some 300 unique factor IX mutations have been identified.

The most common inherited bleeding disorder is **von Willebrand disease**, due to the inherited deficiency in von Willebrand factor (**vWF**). vWF has two roles in clotting. First, the adhesion of platelets to collagen exposed on endothelial cell surfaces is mediated by vWF. vWF acts as a bridge between a specific glycoprotein on the surface of the platelets (GPIb/IX) and collagen fibrils. vWF also binds to and stabilizes factor VIII in the plasma. Persons deficient in vWF will also have a concomitant decrease in plasma factor VIII. Clinically significant von Willebrand disease occurs in about 125 persons per million, about twice the frequency of hemophilia A.

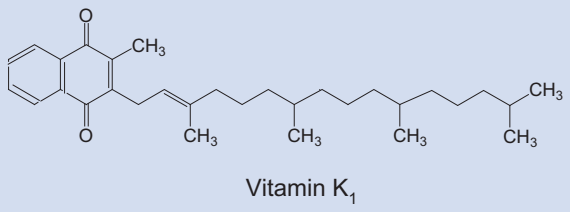
Clinical Applications: Anticoagulant Therapy

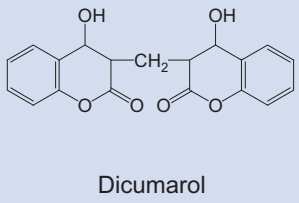
Inappropriate clot formation is a clinical problem as common as hemorrhage. Several agents can be used to prevent clotting. Figure 5.1.5 shows that several of the proteolytic reactions in the clotting cascade require Ca^{2+} ions. These Ca^{2+} ions bind to special γ-carboxyglutamic acid residues on factors II (prothrombin), VII, IX, and X. Chelation of plasma Ca^{2+} by adding Na citrate or Na oxalate prevents these reactions and stops the coagulation cascade. Ca^{2+} chelators can be used to stop coagulation of the blood outside the body, but they cannot be used *in vivo* because the heart and nerves depend on normal plasma [Ca^{2+}] for their operation. The strength of the heart beat decreases directly with decreases in plasma [Ca^{2+}], and ceases altogether when plasma [Ca^{2+}] falls below 0.2 mM.

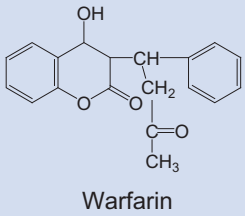
As mentioned in the text, heparin is produced by mast cells and is present on the surface of endothelial cells. It prevents blood clotting by activating antithrombin III some 100- to 1000-fold. During tissue damage, the activation of thrombin outstrips the natural inhibition of it and clot formation occurs. Antithrombin III activity can be stimulated by injecting heparin, which effectively inhibits clot formation.

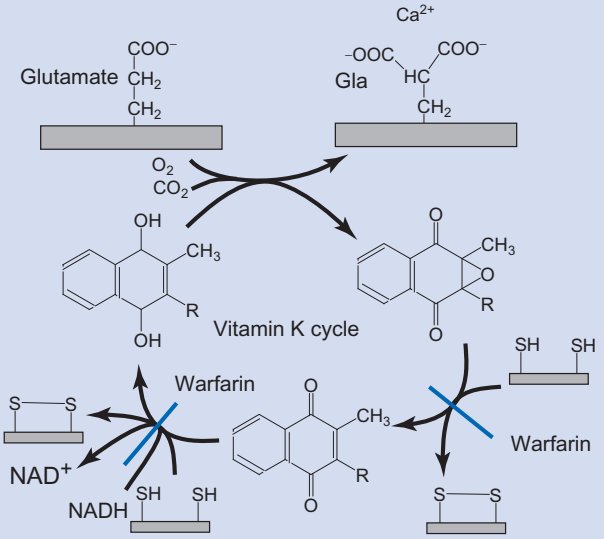
The liver synthesizes clotting factors II (prothrombin), VII, IX, and X. All of these proteins contain γ-carboxyglutamic acid residues, also called gla, near their amino terminus. This amino acid contains two exposed carboxyl groups that bind Ca^{2+}. The γ-carboxyglutamic acid is formed by a posttranslational modification of the proteins that requires vitamin K as a cofactor. Vitamin K was discovered in 1929 by Henrik Dam in Copenhagen when he fed chicks fat-free diets and noted that they developed hemorrhages under the skin and in the muscles. He subsequently discovered that the antihemorrhagic factor was fat soluble but none of the known fat-soluble vitamins could prevent the hemorrhagic disease. Dam named the new vitamin "K" for "koagulation." In 1939 vitamin K was isolated from alfalfa. In 1941, Campbell and Link discovered that bishydroxycoumarin (dicumarol) was the active agent in spoiled clover that caused a hemorrhagic disease of cattle. This compound has structural similarities to vitamin K, and prevents the synthesis of vitamin

K-dependent gla proteins by interfering with the vitamin K cycle, shown below. A second compound, warfarin (named for the Wisconsin Alumni Research Foundation, and known as Coumadin®), also inhibits vitamin K recycling and thereby prevents formation of the vitamin K-dependent clotting factors.









SUMMARY

The cardiovascular system transports nutrients and chemical signals to the tissues and removes waste materials and heat. This transport system is necessary mainly because diffusion is too slow to exchange materials over the distances between our tissues and the environment. The medium of transport is the blood, which normally remains contained within blood vessels. The final exchange of materials occurs across the walls of the capillaries from the blood to the interstitial fluid that bathes all cells of the body. To assure rapid exchange, the blood reaches all parts of the body, coming within short distances of all cells. This is accomplished by an extensive network of vessels. The arteries take blood away from the heart whereas the veins return blood to the heart.

The heart provides the motive force for movement of the blood. It consists of a dual pump. The right heart pumps blood through the pulmonary circulation whereas the left heart pumps it through the systemic circulation. These two circulations are in series, whereas all other organs supplied by the systemic circulation are perfused in parallel. This arrangement allows for the separate regulation of blood flow to the organs to meet demands.

Because the circulatory system is closed, at steady state the output of the right heart must match its input, which in turn must match the output of the left heart. Transient deviations from this balance are accompanied by shifts in blood to or from the systemic circulation into the pulmonary circulation.

Flow through the cardiovascular system is driven by pressure which originates with the beating of the heart. The vascular component of the cardiovascular system can be characterized by two major characteristics: its resistance to flow and its compliance. The resistance relates total flow to the pressure difference that drives the flow, whereas the compliance relates the volume within the vessels to the pressure.

Blood consists of a fluid, the plasma, in which cells are suspended. The fraction of the blood volume occupied by the red blood cells is called the hematocrit.

Blood clotting usually begins with tissue injury that exposes platelets to collagen, which causes the platelets to adhere together, and release signaling molecules including serotonin, ADP, TXA_2, and a lipoprotein factor that hastens coagulation. The key reaction in coagulation is the conversion of fibrinogen to fibrin and its cross-linking into a dense network of fibers. Thrombin is a serine protease that converts fibrinogen to fibrin, and its activation from prothrombin involves a complicated cascade of events. The body contains anticoagulants to prevent accidental clotting. Once formed, clots retract and then are dissolved by plasmin, which is activated from plasminogen by proteolysis.

REVIEW QUESTIONS

1. What is convection? Why is it important?
2. Define vascular resistance. How, in general, does it depend on vessel caliber?
3. How is the pulmonary circulation distinct from the systemic circulation?
4. Define compliance. Why is compliance higher in the veins than in the arteries?
5. What enzyme converts fibrinogen to fibrin? How is it activated?
6. What enzyme dissolves clots? How is it activated?