

## II. Organ System Physiology

### 4. CARDIOVASCULAR PHYSIOLOGY

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#### BLOOD

##### 1. What are the components that make up blood?

Blood is a two-phased fluid consisting of formed cellular elements suspended in a liquid medium, the plasma. The formed elements are red cells (erythrocytes), white cells (leukocytes), and platelets.

##### 2. What are the parts of the plasma?

The plasma, or fluid fraction of the blood, normally occupies about 55% of the blood volume. The normal concentrations of some of the constituents of plasma are as follows:

	PLASMA (mOsm/L OF H <sub>2</sub> O)
Na <sup>+</sup>	142
K <sup>+</sup>	4.2
Ca <sup>++</sup>	1.3
Mg <sup>+</sup>	0.8
Cl <sup>-</sup>	108
HCO <sub>3</sub> <sup>-</sup>	24
HPO <sub>4</sub> <sup>-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	2
SO <sub>4</sub> <sup>-</sup>	0.5
Amino acids	2
Creatine	0.2
Lactate	1.2
Glucose	5.6
Protein	1.2
Urea	4
Others	4.8
Total mOsm/L	301.8
Corrected osmolar activity (mOsm/L)	282.0
Total osmotic pressure 37°C (mmHg)	5443

##### 3. What is the hematocrit?

If a blood sample from an adult is centrifuged in a graduated test tube, the relative volume of the packed red cells is termed the *hematocrit*. For a normal adult, this volume is about 40–45% of the total. That is, the red cells occupy about 40–45% of the total volume of the blood in the body. The white blood cells, which are less dense than the red cells, form a thin layer (the so-called buffy coat.) The remaining 55–60% of the volume is the plasma. An increase in hematocrit occurs in people acclimatized to high altitude, where there is an associated decrease in oxygen level. The hematocrit in this case can be 60–65% of the total blood volume.

#### 4. How many red blood cells are there?

In a normal adult, there are between 4.5 million and 6 million red blood cells per milliliter of peripheral blood. More than the normal red cell volume or a greater hematocrit is known as **polycythemia**. A decreased hematocrit is known as **anemia**.

#### 5. How many white blood cells are there?

The number of white cells in the circulation can be quite variable. In a normal individual, there are between 5000 and 10,000 white blood cells per milliliter of normal peripheral blood. The white cells are mainly involved in the immune process. Thus, an infection normally results in an increase in white cells known as **leukocytosis**. A reduction in white cells below the normal level is known as **leukopenia**.

#### 6. How many platelets are there in the circulation?

There are about 150,000–300,000 platelets per milliliter in normal peripheral blood. Because of their small size (2–3  $\mu$ ), they make up only a small fraction of the blood volume. Platelets are involved in blood coagulation.

#### 7. What is the blood volume of a normal person?

The normal blood volume of an adult remains constant over time, but there is considerable variation from one person to another. The values in a normal adult generally range from 70 to 75 mL per kilogram of body weight. Thus, a 70-kg adult might have a total blood volume of about 5000 mL. About 55%, or 2750 mL, of this blood volume is plasma, and about 45%, or 2250 mL, is total red cell mass. One situation in which blood volume is dramatically increased is in pregnancy. Blood volume can increase to nearly 50% above baseline by about 32 weeks, whereas the erythrocyte mass increases to about 30% above baseline.

#### 8. How does the blood carry oxygen?

The vast majority of oxygen carried in the blood is bound to **hemoglobin**, a protein consisting of globin, four polypeptide chains attached to four iron-containing **heme** groups, which are the binding sites for oxygen. Hemoglobin is the primary constituent of the erythrocyte and combines reversibly with oxygen to form **oxyhemoglobin**. In normal whole blood, the concentration of hemoglobin is about 15 g/dL. When blood is exposed to high oxygen pressure, all the hemoglobin combines with oxygen to form oxyhemoglobin. Under these conditions, the hemoglobin is said to be **fully saturated**. Fully saturated hemoglobin can accommodate about 1.39 mL of oxygen per gram of hemoglobin. Thus, blood with a hemoglobin concentration of 15 g/dL has an oxygen capacity of about 20.8 mL/dL of blood, or 20.8 volume percent. The amount of oxygen that is carried by hemoglobin depends on the partial pressure of oxygen ( $PO_2$ ) to which the hemoglobin is exposed. This relationship is defined by the **oxygen dissociation curve**. Under normal conditions, the  $PO_2$  level found in the lungs results in blood being about 97% saturated. In this case, when arterial blood has a hemoglobin concentration of 15 g/dL, the oxygen content is about 20 mL/dL.

#### 9. What is the venous oxygen content after the blood has given up oxygen to the tissues?

When the blood has reached the large veins, a lot of the oxygen has been given up to the tissues. Blood in the large veins is referred to as **mixed venous blood**, and its  $PO_2$  value falls to about 40 mmHg. This mixed venous blood has an oxygen saturation of about 75% and therefore a blood oxygen content of about 16 mL/dL. Under this condition, blood releases about 4 mL of oxygen for each 100 mL of blood flow to the tissues.

#### 10. What other factors determine the oxygen content of the blood?

pH,  $PCO_2$ , temperature, and the concentration of 2,3-diphosphoglycerate (2,3-DPG) may cause a shift in the oxygen hemoglobin dissociation curve and cause the additional

unloading of oxygen from hemoglobin. Decreased pH, increased  $PCO_2$ , increased temperature, and increased 2,3-DPG all cause a rightward shift of the oxyhemoglobin dissociation curve, which allows more oxygen to be unloaded at the level of the tissues. Conversely, the presence of fetal hemoglobin shifts the curve to the left, which aids in oxygen delivery to fetal tissues.

#### 11. How do white blood cells contribute to the properties of blood?

Although white blood cells represent only a small portion of the cells in the blood, they may have a great effect on the ability of the blood to flow through the vessels. Because white cells are rather large and stiff, and because under some conditions they may stick to the venular endothelial cells, white blood cells can contribute dramatically to the resistance of blood flow. Although under normal conditions the contribution of white cells to the viscosity of the blood is small, under conditions when white cell counts become high, this effect may be dramatic and may cause large increases in vascular resistance.

#### 12. How much do the red blood cells affect the viscosity of the blood?

Under normal conditions in which the hematocrit is about 40%, the contribution of red blood cells to the viscosity of blood is relatively small. A rise in the hematocrit ratio from 40% to 70%, which may occur in polycythemia, can increase the viscosity more than twofold, with direct effect on the resistance to blood flow. This increase in resistance is quite large and may cause a substantial effect on the arterial blood pressure.

#### 13. What is the difference between viscosity and shear stress?

Viscosity may be thought of as the thickness of the blood or the difficulty in forcing it to flow through a tube. Because blood is composed of a suspension of formed elements and plasma, the viscosity of the blood varies as a function of the hematocrit. Increasing hematocrit causes an increase in viscosity. Normal blood has a viscosity that is about 2.5 times that of water. That means that about a 2.5 times greater pressure drop is required to drive the same amount of blood through a given tube as it would for water.

Shear stress is the force that the blood exerts on the vessel wall as it flows. The greater the rate of blood flow in a vessel, the greater the force on the vessel wall, or the shear force. This shear force is important because it is the force sensed by endothelial cells that line the blood vessel. It has been suggested that shear sensitivity is a major mechanism by which endothelial cells sense their environment and alter such functions as permeability of the vascular wall and biosynthetic activity of endothelial cells.

#### 14. What is a blood type?

Blood type refers to the presence of antigens on the surface of red blood cells. Hundreds of such antigens have been found in human blood cells, but most of them are weak. Two antigens—type A and type B—occur on the surfaces of red blood cells and are those commonly measured in blood typing. Another antigen, the **type D Rh antigen**, is the basis for most Rh typing. A person who has the D antigen is said to be **Rh positive**, whereas a person who does not have the D antigen is said to be **Rh negative**. There are antibodies in the plasma that can interact with the antigens on the red cells to cause agglutination. Because of this, the antigens are referred to as **agglutinogens**, and the antibodies are referred to as **agglutinins**. In general, transfusions are made with the same type of donor blood as that of the recipient. However, type O blood has no agglutinogens to be agglutinated, and therefore type O blood can be given to any recipient. Type O is called the **universal donor blood**. Conversely, type AB individuals have no agglutinins in their plasma; therefore type AB plasma is referred to as **universal plasma**, and type AB subjects are called **universal recipients**. The agglutinogens, agglutinins, and percent of the population that have each blood type are shown below:

BLOOD TYPE	AGGLUTININOGEN	AGGLUTININ	RH ANTIGEN	PERCENT IN POPULATION
A positive	A	anti B	present	
A negative	A	anti B	absent	36.0
B positive	B	anti A	present	6.0
B negative	B	anti A	absent	8.5
O positive	none	anti A and B	present	1.5
O negative	none	anti A and B	absent	37.0
AB positive	A and B	none	present	7.0
AB negative	A and B	none	absent	3.4
				1.0

### 15. How does blood clot?

An injury to a vessel disrupts the endothelium and results in exposure of connective tissue, including collagen. Platelets are attracted to the collagen, where they adhere and are triggered to release adenosine diphosphate (ADP) and a prostaglandin, **thromboxane A<sub>2</sub>**. These substances attract more platelets and cause the adhered platelets to become "sticky," so new platelets adhere to the old ones and a platelet plug is formed. If the injury is small, this plug may be sufficient to stop bleeding. However, with a larger injury, a clot may be needed. A clot results from a cascade of activation of thirteen factors that circulate in inactive form in the plasma. The final steps of the cascade are conversion of **prothrombin** (plasma protein) to **thrombin** by activation of **factor X** in the presence of calcium. Thrombin converts **fibrinogen** (soluble plasma protein) to **fibrin** (insoluble strands). Strands of fibrin combine to form a network that traps red blood cells and platelets, producing a clot. Activation of factor X can result from activation of either an intrinsic or extrinsic clotting pathway. The intrinsic pathway consists of factors that are all present in blood, whereas the extrinsic pathway includes release of **tissue thromboplastin** from damaged tissues. For the intrinsic pathway, exposure of plasma to collagen activates a plasma protein called factor XII, which triggers a cascading activation of other factors leading to activation of factor X. For the extrinsic pathway, tissue thromboplastin serves as the initiating factor for the cascade of activation. Vitamin K is a necessary contributor to clotting, because it is required for production of many clotting factors by the liver.

### 16. What is hemophilia?

**Hemophilia** is an inherited genetic disorder that is linked to the X chromosome. Blood from hemophiliacs is slow to clot, due to delayed formation of fibrin. Hemophilia A results from a defective factor VIII, whereas hemophilia B results from a defective factor IX (Christmas factor).

### 17. How do anticoagulants work?

Common anticoagulants are **heparin** and the **coumarin** derivatives **warfarin** (Coumadin) and **dicumarol**. Heparin prevents clotting by activating a plasma protein called antithrombin III, a serum protease inhibitor that prevents activation of needed serum proteases at several steps in the clotting cascade process. Coumarin derivatives are competitive inhibitors of vitamin K that prevent the vitamin-induced production of clotting factors by the liver. Dicumarol was the first anticoagulant that could be administered to humans orally. The successor to dicumarol was warfarin, which first became known after it was introduced as a rodenticide. Warfarin's effectiveness led to its widespread success, and it has become the most widely prescribed anticoagulant drug in the nation. Anticoagulants do not break up clots that already have formed in the vessels.

### 18. How does aspirin "thin" the blood?

Aspirin does not actually thin the blood, but it does interfere with the production of **thromboxane A<sub>2</sub>**, a platelet aggregator. Therefore, aspirin will decrease the ability of platelets to adhere to each other and form a platelet plug.

## HEART

## 19. What is the basic anatomy of the heart?

The heart comprises two separate pumps: a right heart and a left heart. The right heart pumps the blood through the lungs, and the left heart pumps the blood through the peripheral organs. Each side of the heart, the right and the left, is composed of two pumps in series: one is the atrium and the other is the ventricle. The role of the atrium is primarily to move the returning blood rapidly into the ventricle to propel the blood through either the pulmonary or the systemic circulation. Intrinsic mechanisms within the heart provide the rhythmicity of the cardiac muscle to cause the heart's constant beating.

## 20. What are the major types of cardiac muscle?

- Atrial muscle
- Ventricular muscle
- Purkinje fibers, a specialized type of conductive fiber found in the walls of the ventricles

## 21. How do cardiac muscles contract?

Contraction of atrial and ventricular cardiac muscle is similar to that of skeletal muscle, except that the duration of the contraction is much longer and that some of the calcium that participates in contraction enters as a current-carrying ion during depolarization. The conductive fibers of the heart do not contract significantly; however, they provide pathways for the electrical activation to spread throughout the heart.

## 22. What is responsible for the spontaneous rhythmic excitation of the heart?

Virtually all of the contractile and electrical generating cells in the heart are capable of spontaneous excitation. Specialized cells within the sinoatrial (SA) node, which is located in the superior lateral wall of the right atrium, have the highest rate of spontaneous activation. These cells determine the intrinsic heart rate.

## 23. What is the mechanism of the sinus node rhythmicity?

Pacemaker activity of cells of the SA node is due to a slowly increasing inward current of calcium, which slowly depolarizes the cells. This slow depolarization takes the cells from a resting membrane potential of only about  $-55$  mV to a threshold potential of  $-40$  mV, at which point other channels become activated. This leads to a rapid entry of both calcium and sodium ions, causing an action potential. Repolarization occurs when the sodium channels become inactivated and potassium channels open.

## 24. How is the cardiac action potential transmitted throughout the heart?

The electrical discharge from the SA node travels outward from the node and across the atrial muscle mass at a velocity of about 0.3 m/s. Because the ventricles are electrically isolated from the atria, the depolarization from atrium to ventricle must travel through a specialized conductive route. This pathway is known as the atrioventricular (AV) node and is located in the posterior septal wall immediately behind the tricuspid valve. Transmission of the electrical impulse through the AV node occurs only in one direction from the atrium to the ventricle and introduces a delay of approximately 100 ms, which allows time for the ventricles to fill after atrial contraction. Once the depolarization passes through the AV node and into the ventricles, it is carried by a specialized conductive system known as the Purkinje fibers. These fibers carry the depolarization rapidly throughout the ventricle, resulting in a uniform contraction of ventricular muscle.

## 25. How is the rhythmicity of the heart controlled?

The heart is supplied with both sympathetic and parasympathetic nerves. The parasympathetic nerves, which run in the vagus, are distributed mainly to the SA node and the AV node. The sympathetic nerves are distributed throughout the heart.

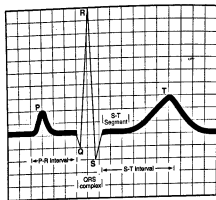
Stimulation of parasympathetic nerves to the heart decreases the rate of depolarization of the SA node and slows the rate of conduction across the AV node. Parasympathetic nerve stimulation causes an increase in potassium conductance, which slows the rate of depolarization and lowers the resting membrane potential of the nodal cells. These changes result in generation of a slower heart rate.

Sympathetic stimulation causes the opposite effects on heart rate by increasing the spontaneous rate of firing of the SA node, reducing the delay across the AV node and increasing the speed of force of contraction of cardiac muscle. Sympathetic stimulation produces an increase in calcium conductance, which increases the rate of depolarization and raises the resting membrane potential of nodal cells. These changes result in generation of a faster heart rate.

## 26. What is an electrocardiogram (ECG)?

The ECG is a record of the electrical activation of the heart. It represents a summation of the action potentials of the individual cardiac cells. As this wave of excitation progresses through the heart, the area that is depolarized is electrically negative relative to the resting muscle (which is yet depolarized). This makes the heart a dipole, or an electrical source consisting of areas of locally distributed electrical charge. Due to the ions present in body fluids and structures, the body acts as a volume conductor, which allows the electrical activity generated by the heart to be conducted to the surface of the body. This permits the electrical currents generated by the heart to be recorded on surface electrodes, resulting in recording of the ECG. The ECG represents a well-characterized pattern of activity produced by the sequence of depolarization-repolarization of the cardiac muscle. The normal ECG is composed of the following:

- **P-wave**, which represents atrial depolarization (80–100 ms)
- **QRS complex**, which represents ventricular depolarization (60–100 ms)
- **T-wave**, which represents ventricular repolarization (100–250 ms)



A typical electrocardiogram (ECG) showing the prominent waves and intervals. Scale for the tracing is the adopted for conventional clinical recordings, with vertical lines spaced at 0.4-sec intervals and horizontal lines representing 0.1 mV increments.

Heart rate is often estimated by the **R-R interval**, or the time that occurs between the R-waves of sequential beats in the ECG. The R-wave is selected because it is one of the most striking features of the ECG. The appearance of the ECG is greatly influenced by the positions of the leads on the surface of the body, and thus twelve conventional arrangements have been adopted to standardize the lead arrangements.

- Three standard limb leads, which are bipolar recordings because they display the difference in electrical activity between two different points on the body:
  - Lead I—Electrodes on the right arm and left arm
  - Lead II—Electrodes on the right arm and left leg
  - Lead III—Electrodes on the left arm and left leg

- **Three augmented limb leads**, which are unipolar recordings because they record voltages at only one point on the body relative to an indifferent reference point:
  - AVR—Electrode on right arm
  - AVL—Electrode on left arm
  - AVF—Electrode on left leg
- **Six precordial leads**, which are unipolar recordings in which the active electrode is placed at one of six positions in an arc pattern on the chest around the heart, starting at  $V_1$ , located in the fourth intercostal space just to the right of the sternum, and ending at  $V_6$ , located in the fifth intercostal space at the left midaxillary line

### 27. What is the structure of cardiac muscle?

Cardiac muscle differs from skeletal muscle in that the cardiac muscle fibers are arranged like a latticework. The fibers divide then recombine to form what is known as a syncytium. Similar to skeletal muscle, cardiac muscle is striated and contains typical myofibrils made up of actin and myosin filaments.

### 28. What is the significance of the syncytial nature of cardiac muscle?

From a functional point of view, the syncytial nature of cardiac muscle provides easy movement of cardiac action potentials so that when one cardiac cell becomes excited, the action potential spreads to all the adjoining cells, moving from one cell to another throughout the entire heart chamber. The atrial syncytium and the ventricular syncytium are actually separated from one another by a ring of fibrous tissue around the valvular openings. Normally, action potentials are not conducted from the atrium into the ventricle except through the Purkinje system.

### 29. What is the nature of the cardiac action potential?

Similar to skeletal muscle, the cardiac action potential represents a depolarization from the resting membrane potential. The magnitude of this action potential in cardiac muscle is approximately 105 mV. The most important feature of the cardiac action potential is a long plateau phase of up to 300 ms, which provides time for cardiac filling.

### 30. What is the refractory period of cardiac muscle?

The interval of time during which normal cardiac impulses cannot reexcite an area of cardiac muscle. The normal refractory period of the left ventricle is about 250 ms. This period is important because it ensures that the wave of electrical activation passes in an organized fashion to cardiac muscle, allowing the individual muscle cells of each chamber to contract almost as a single unit, or a "functional syncytium." This produces an efficient contraction to eject blood. If damage occurs to parts of the conducting pathway (myocardial infarction) or the heart becomes enlarged (heart failure), conduction may follow an abnormal pathway, and the refractory periods of the muscle cells may no longer line up with respect to time. The wave of depolarization may then affect areas of the heart out of synchrony, leading to inefficient contractions or even arrhythmias.

### 31. What are the phases of the cardiac contraction?

- **Systole**—the period during which cardiac contraction occurs
- **Diastole**—the period during which relaxation and filling occur

### 32. During what phase of cardiac contraction is the volume in the heart the greatest?

The cardiac chambers fill during diastole; therefore, volume of the heart is at a peak at the end of diastole.

### 33. Why is the left ventricular wall so much thicker than the right ventricular wall?

The thickness of the walls of the cardiac chambers is indicative of the work that they must do to pump the blood into their respective circulations. The pressure in the systemic circulation is significantly higher than that of the pulmonary circulation, although the blood flow through both

circulations is equal. Thus, the left ventricle needs a larger muscle mass to overcome the higher pressures in the systemic circulation.

### 34. What are the pressures in all of the chambers of the heart?

The **right atrium** is a highly compliant chamber that serves to absorb the blood as it moves from the systemic circulation to return to the heart. Because of its high degree of compliance and the weakness of its contraction, the pressure within the right atrium does not change much. As the chamber fills, pressure rises from approximately 0 to about 6 mmHg with a mean of approximately 4 mmHg.

The **right ventricle**, which pumps the blood into the pulmonary artery, has higher pressures, ranging from 0 mmHg diastolic to 25 mmHg systolic pressure. Pressures in the pulmonary artery range from approximately 4 mmHg during diastole to approximately 28 mmHg at the peak of systole.

Blood returning from the pulmonary circulation enters the **left atrium**. Similar to the right atrium, the left atrial pulse pressure is small with a mean pressure of approximately 8 mmHg.

Blood leaves the left atrium and enters the **left ventricle**. The left ventricle pumps the blood into the aorta and the rest of the systemic circulation; therefore, pressures in the left ventricle range from approximately 125 mmHg during the peak of systole to approximately 8 mmHg during diastole. Aortic pressure normally ranges from approximately 120 mmHg systolic to 80 mmHg diastolic pressure.

### 35. What are the functions of the valves of the heart?

The valves in the heart separate the atria from the ventricles (**AV valves**) and the ventricular chambers from the circulations (**semilunar valves**) into which they pump. The valves on the right side are the **tricuspid valve** and the **pulmonary semilunar valve**. Those on the left side are the **mitral (bicuspid) valve** and **aortic semilunar valve**. Because the valves open only in one direction, they force the blood to be propelled out of the heart during contraction. Valve defects or damage to the valves may cause reflux of blood from the circulation back into the heart or from one chamber to another, resulting in inefficient delivery of blood from the heart to the circulation. Backward reflux from the leaking valve may be heard as a **heart murmur**.

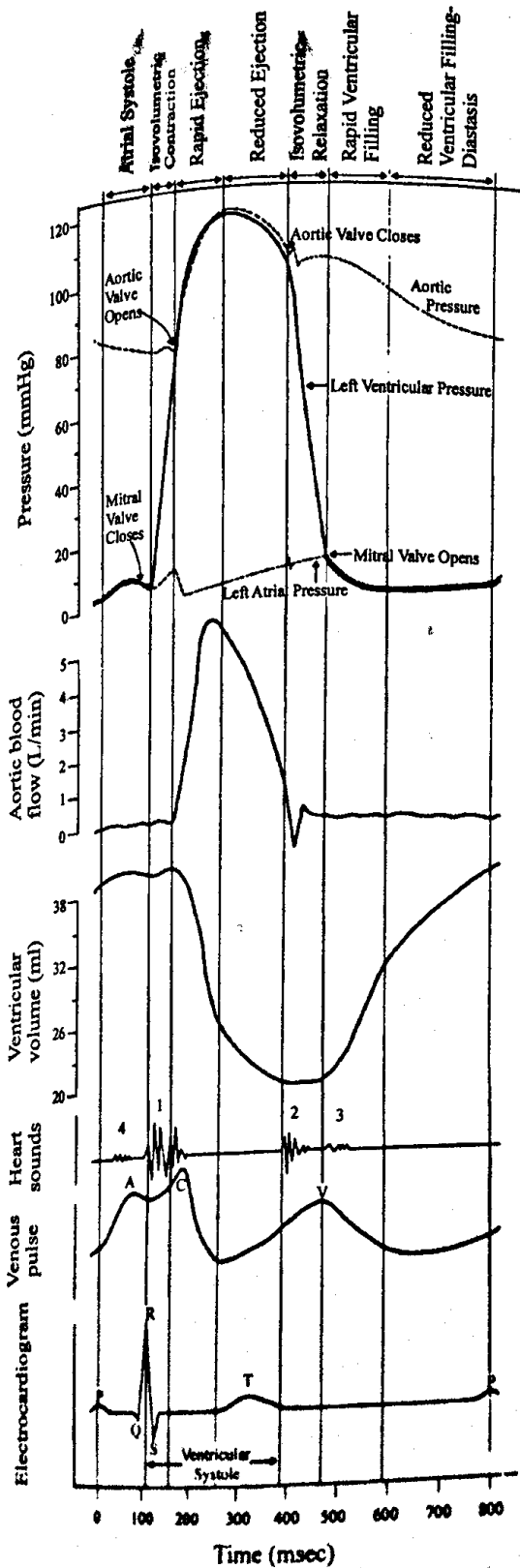
### 36. What are the functions of the papillary muscles?

The **papillary muscles**, which arise from the inner wall of the ventricle, are connected to the valve leaflets via tendinous structures known as the **chordae tendinae**. During cardiac contraction, as the ventricle decreases in size, contraction of the papillary muscles helps to maintain the proper positions of the valve leaflets and prevent the valves from inverting at higher pressures.

### 37. What are the key features of the cardiac cycle?

The events of the cardiac cycle are summarized in the accompanying figure for the left side of the heart (see figure, next page). Similar events occur for the right side of the heart, but the pressures are all reduced accordingly. **One cardiac cycle** refers to the period comprising the beginning of one heart beat through the beginning of the next heart beat. The cardiac cycle is initiated by the spontaneous generation of an action potential in the SA node. This action potential spreads across both atria resulting in atrial contraction and a rise in atrial pressure (atrial systole). This increase in atrial pressure ejects blood into the left ventricle. As the depolarization spreads through the AV bundle into the ventricles, the ventricles contract with a delay of approximately 100 ms after the atrial contraction. Ventricular pressure increases, resulting in closure of the mitral valve and a period of **isovolumetric contraction**, when the ventricular muscle begins to contract but both valves are closed. Ventricular contraction results in a rise in pressure within the ventricular chamber and when ventricular pressure exceeds aortic pressure, the aortic valve opens and ejection of the blood into the aorta occurs (rapid followed by slower ejection). After ejection, the cardiac muscle begins to relax and pressure drops, allowing the aortic valve to close (isovolumetric relaxation). When pressure within the ventricle falls below that of atrial pressure, the mitral valve opens and ventricular filling begins (rapid followed by slower ventricular filling), preparing the heart for the next beat.





Depiction of the events of the cardiac cycle demonstrating the relationships between the electrical and mechanical events. The upper panel shows the left atrial, left ventricular, and aortic pressures. Note that left ventricular and aortic pressure are equal to each other only during the ejection phase when the aortic valve is open. The aortic blood flow tracing in the second panel illustrates the pulsatile nature of cardiac output and shows that, for the majority of the cardiac cycle, blood flow leaving the heart is zero. Finally, as can be seen by comparing the electrocardiogram in the lower panel with the volume tracing above, changes in electrical activity precede mechanical changes in the heart that lead to contraction.

38. How much of the oxygen required for cardiac contraction comes directly through the ventricular wall as opposed to from the coronary circulation?

Although the left atrium and left ventricle are carrying highly oxygenated blood in large amounts, virtually none of the oxygen required for the cardiac contraction diffuses through the wall of the ventricle. Similar to other tissues, the heart has a complete circulation known as the coronary circulation. As in other vascular beds, coronary vessels branch, ultimately forming capillaries where oxygen exchange occurs. Complete blockage of coronary vessels causes regions of the heart to receive no oxygen and therefore ultimately to die, leading to a myocardial infarction.

39. Explain Starling's law of the heart.

The Frank-Starling mechanism, or Starling's law of the heart, describes the intrinsic ability of the heart to adapt to changes in the amount of blood returned to it by the systemic circulation. The Starling mechanism operates on the principle that as cardiac muscle is stretched, its ability to contract is augmented. Thus, when an extra amount of blood returns into the ventricles, the cardiac chambers are stretched, resulting in a more vigorous contraction that propels the extra blood out of the heart. This relationship between the filling of the heart and the cardiac output is often quantified by graphing filling pressure or preload against cardiac output in a graph referred to as the cardiac function curve. The mechanism ensures that both ventricles pump the same volume of blood within one beat, preventing any overfilling of the pulmonary or systemic circulations.

40. Clarify the distinction between preload and afterload

**Preload** refers to the pressure or stretch of the cardiac chambers during diastole. Therefore, preload is the load on the heart prior to contraction. Increases in preload cause more vigorous cardiac contractions by the Frank-Starling mechanism.

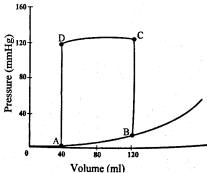
**Afterload** is the pressure or resistance into which the heart pumps. Thus, afterload is the magnitude of the load the heart must overcome to eject blood. We often refer to the arterial or pulmonary pressure as the afterload for the left and right ventricles, respectively.

41. Is the preload for the right ventricle equal to the preload for the left ventricle?

Cardiac output from both the left and the right heart is matched; that is, it is equal. The left heart operates at a significantly elevated filling pressure because left ventricular afterload (systemic arterial pressure) is greater than right ventricular afterload (pulmonary arterial pressure).

42. What is a pressure volume loop?

The pressure volume loop charts the changes in ventricular pressure and volume throughout one beat of the cardiac cycle. The element of time is not considered in a pressure volume loop. As shown in the accompanying figure of the left ventricle, one loop represents one beat.



- Beginning at point A and proceeding in a counterclockwise direction around the loop, we move first through the phase in which the left ventricle is filling without a large rise in pressure. This is the **filling phase**.
  - At point B, the left ventricle begins to contract, which leads to mitral valve closure; however, the aortic valve has not yet opened, so the period between B and C is the **isovolumetric contraction phase**.
  - At point C, the aortic valve opens when sufficient pressure has been generated to overcome aortic pressure, and blood is pumped from the ventricle into the aorta. The period of time from point C to point D is the **ejection phase**.
  - At point D, the ventricle has begun to relax, and the pressure rapidly falls, resulting in the closure of the aortic valve. The mitral valve remains closed until point A, at which point left atrial pressure exceeds ventricular pressure and the valve opens to permit filling. Thus, the phase between D and A is the **isovolumetric relaxation phase**.
- The segments B-C and C-D represent systole, whereas the segments D-A and A-B represent diastole.

#### 43. Put the work of the heart in perspective.

The heart pumps out about 2.5 ounces of blood on every beat. Each day it pumps at least 2500 gallons, which is nearly 10,000 L of blood. This amount of blood weighs 20 tons. The average adult heart beats 70–75 times a minute. Generally, the smaller the size of the heart, the faster the heart beats; thus women's hearts in general beat six to eight times per minute more than men's hearts do.

#### 44. What is the medical term for a heart attack?

Myocardial infarction.

#### 45. What is a heart attack?

Some of the heart muscle cells die as a result of reduced blood flow through one of the main arteries (often because of arteriosclerosis). The outlook for a patient depends on the size and location of the blockage and the extent of the damage. In the United States, 33% of patients who have a heart attack die within 20 days. It is the leading cause of death in the United States.

#### 46. What is cardiac contractility?

Cardiac contractility is a measure of the performance of the heart at a given preload and afterload. It may be defined precisely as the change in peak isometric force at a given initial fiber length. Contractility is an index that measures the ability of the heart to pump blood. It should not be confused with a direct measurement of the force of cardiac contraction because that depends strongly on the preload (Frank-Starling mechanism). There are several possible operational definitions of contractility:

1. The slope of the cardiac function curve
2. The plateau level of the cardiac function curve
3. The maximal rate of change of left ventricular pressure during systole ( $dp/dt_{max}$ )

Clinically the ejection fraction is often used as a measure of contractility; however, no index is entirely satisfactory under all conditions.

#### 47. What is ejection fraction?

The percentage of blood pumped by the heart on each beat. It is defined as the volume of blood ejected by one ventricle in one beat (**stroke volume**) divided by the total amount of blood within the ventricle prior to contraction (**end-diastolic volume**). A normal ejection fraction is about 60%.

#### 48. What is the relationship among cardiac output, heart rate, and stroke volume?

$$\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}$$

The **stroke volume** is determined primarily by the preload as defined by Starling's law of the heart. That is, as preload increases, stroke volume also increases until the stroke volume reaches a plateau. Stroke volume also can be increased by sympathetic stimulation of the heart. Heart rate changes primarily in response to parasympathetic and sympathetic influences on the heart. Increases in both heart rate and stroke volume can cause increases in **cardiac output**, the amount of blood ejected by one ventricle per minute.

**49. What is the relationship between heart rate and cardiac output?**

In general, as heart rate increases, cardiac output increases. When heart rate begins to get high (> 150 beats/min), stroke volume begins to decrease significantly with increasing heart rate. The decrease in stroke volume with increasing heart rate causes cardiac output to begin to fall at high heart rates. The reduction in stroke volume at high heart rates is due to a decrease in the length of time the heart spends in diastole and thus a reduction in the time available to the heart for filling.

**50. What is the use of the cardiac function curve?**

Because cardiac output is proportional to stroke volume and end diastolic pressure is proportional to right atrial pressure, we can create a graph that tells us the pumping ability of the heart is a function of its filling pressure. This cardiac function curve is a useful tool that determines the preload sensitivity of the heart in determining cardiac output.

**51. How does the cardiac function change as contractility changes?**

Under normal conditions, the cardiac function curve may change both slope and plateau level; an increase in slope or an increase in plateau level corresponds to an increase in contractility of the heart, whereas a decrease of slope or a decrease in the plateau level corresponds to a decrease in contractility. This contractility also is a measure of the pumping efficiency of the heart.

**52. What is stroke work?**

**Stroke work** is the amount of work done by the heart on each beat, proportional to the area of the pressure volume loop. An approximation for stroke work is obtained by multiplying stroke volume times arterial pressure. The higher the pressure or the higher the stroke volume, the larger the work done by the heart. Stroke work is also a function of preload because the stroke volume increases as preload increases. In fact, the amount of work done by the right and left ventricle differs not because the stroke volume differs, but because the load into which each ventricle pumps is different. The right ventricle pumps into a low pressure in the pulmonary artery, resulting in a small amount of work, approximately 9 g-m. The left heart pumps into a significantly higher load in the aorta; therefore, for the same stroke volume, its work is much greater, approximately 30 g-m. Thus, even though the output of a left heart and right heart is equal, stroke work is much greater for the left heart because of the greater afterload.

**53. If increases in preload increase cardiac output, what do increases in afterload do to cardiac output?**

Both the left ventricle and the right ventricle are sensitive to changes in afterload. Increasing afterload decreases stroke volume and therefore decreases cardiac output. Under conditions in which cardiac output is compromised, either by high afterload or by reductions in cardiac function, one of the most effective means for increasing cardiac output is by using afterload reduction. One interesting feature of the heart is that despite the fact that the right and left ventricle are independently afterload-sensitive, the entire heart-lung compartment is remarkably resistant to reductions in stroke volume caused by increases in arterial pressure. It is resistant because as arterial pressure afterload is increased for the left ventricle, the right ventricle continues to pump blood through the pulmonary circulation, causing an increase in left ventricular preload and the a compensation for the increase in left ventricular afterload. This compensation results in a normalization of the blood flow through the heart.

54. How do the mechanical properties of the heart change as it goes from diastole to systole?  
 During diastole, when the heart is in a relaxed state, its compliance is large, making it easy for the heart to fill with blood. As systole begins, the cardiac muscle shortens, but it also stiffens, causing a reduction in compliance and a stiffening of the heart. This change in the mechanical properties of the heart is important because diastolic filling is maximized when the compliance is high and it is easy for the heart to fill with blood. Ejection of the blood, which occurs in systole, is maximized as the heart shortens and stiffens.

55. Are there conditions when the properties of the heart do not change from diastole to systole?

Yes. Immediately after periods of ischemia in the heart, when significant damage occurs to the cardiac muscle, the ischemic region may not change its mechanical properties. Under this condition, as the heart moves into systole, the region that is ischemic remains highly compliant and may bulge out, forming an aneurysm as the pressure in the ventricle increases. Instead of moving out of the aortic outflow tract, blood moves into the aneurysm. During diastole, the blood cycles back into the heart. This bulging of the cardiac muscle can result in a reduced cardiac output as well as potential damage to the wall of the heart. After some time goes by, that region of the wall may form a scar, which has a much decreased compliance (i.e., an increased stiffness), and even though that part of the wall may not contract, it no longer bulges.

56. What is heart failure?

A reduction in cardiac function that can be caused by a metabolic impairment in the heart, an anatomic malformation, elevated arterial or pulmonary pressure, or cardiac ischemia. Heart failure results in a reduction in cardiac output, which sometimes may be compensated for by an increase in preload. Heart failure is often treated by using drugs that increase contractility, decrease preload, and decrease afterload.

57. Why does exercise training cause a reduction in resting heart rate?

Exercise training results in an increase in the size of the heart, which is known as hypertrophy. In dynamic exercise training, the hypertrophy occurs in such a way as to increase the size of the cardiac chamber. Because the metabolic needs of the body at rest have not changed dramatically, the resting cardiac output remains constant; therefore, the product of stroke volume and heart rate is constant. Because the heart is larger, stroke volume is increased. If stroke volume is larger, heart rate is lower.

58. Why is a reduction in resting heart rate beneficial?

During exercise performance, cardiac output must increase from approximately 5 L/min to nearly 35 L/min, an increase of nearly sevenfold. An increase in heart rate from a low level of 50 beats/min to a high level of 200 beats/min produces a fourfold increase in cardiac output. Under these conditions, stroke volume needs only to double to get an additional factor of two. If the resting heart rate were not reduced, the individual would quickly reach the point at which increases in heart rate would cause reductions in stroke volume, and it would be difficult to increase cardiac output to the required level.

59. What else does an exercise training program do to the cardiovascular system?

Exercise training also affects the vasculature. Increased use of skeletal muscle results in a growth of capillaries in the skeletal muscle, known as angiogenesis. This increase in capillary density increases the availability of oxygen to the skeletal muscle, thus reducing the rate at which skeletal muscle fatigues during exercise performance. In addition, the larger vessels improve in their ability to dilate, thus also facilitating the delivery of blood to working muscle during exercise.

60. What commonly used diagnostic tests are available for evaluating cardiac function?

Echocardiography, gamma scanning, and cardiac catheterization.

### 61. What is cardiac catheterization?

Cardiac catheterization is the introduction of a catheter directly into the heart to assess the pressures and flows in the cardiac chambers. The catheters may be introduced either from the venous side of the circulation through the femoral vein and into the right atrium, the right ventricle, and the pulmonary artery or from the femoral artery advanced into the aorta and the left ventricle. The results of cardiac catheterization can be used to evaluate the contractile force of the left and right ventricles as well as the competence of the valves in the heart. In addition, catheters can be introduced in the coronary arteries and dye injected to visualize the perfusion of the coronary vasculature and to identify regions of the myocardium that may be underperfused.

### 62. What is echocardiography?

Echocardiography is a noninvasive imaging modality based on the echo of sound waves from the walls and valves of the heart. It is useful for detecting wall motion and assessing the competency of the cardiac valves.

### 63. What is a gamma scan or a thallium scan?

Gamma scanning is an imaging technique that relies on the injection of radioisotopes that are taken up specifically by the heart. Once the radioactive material is injected and is taken up by the heart, a special camera known as a gamma camera is used to record the emissions of the radioisotopes. A computer generates an image of the heart that may be interpreted to determine regions that are poorly perfused, shown by an area that has a lack of emission by the radioisotope. A thallium scan is often combined with an exercise test to evaluate changes in perfusion in going from rest to exercise. This combination helps to determine whether a region of ischemia is due to a structural abnormality or to a metabolic abnormality in the heart.

### 64. What does an ECG measure?

An ECG shows the pattern of electrical activation of cardiac muscle. Changes in the ECG from normal indicate problems in conduction of depolarizing activity in the heart, the type of which may be assessed by interpreting the ECG. Although the mechanical function of the heart is not assessed by the ECG, experience allows inferences to be made about mechanical abnormalities that are affected by conduction abnormalities.

### 65. How is the ECG used to show cardiac problems?

Changes in the time needed for cardiac muscle activation or the pathway used for cardiac depolarization, caused by local ischemia or damage to the heart muscle, are reflected by changes in the ECG. For example, atrial tachycardia would be characterized by a decreased R-R interval and increased P, QRS, and T waves. The rate may be high enough to cause coincidence of the T and P waves. A ventricular premature beat would produce a widened QRS complex with an unusual configuration. It would not necessarily interfere with other normal ECG patterns. Decreases in conduction through areas of the heart are shown by prolonged intervals. For example, a conduction slowing at the AV node (first-degree heart block) would result in a prolongation of the P-R interval. Total conduction block (third-degree heart block) at the AV node would result in complete dissociation of P waves and QRS complexes so that there would not be any consistent timing relationship between the two wave forms. A slowing of conduction in the bundle branches of the ventricular depolarization pathway would result in a notched QRS complex, because the synchrony of ventricular depolarization would be lost. Cardiac ischemia often produces an elevation or depression of the S-T segment. Carefully reading the ECG can give insights into cardiac functional problems.

### 66. Is cardiac output determined solely by the heart?

The assumption that if the body needs more blood (e.g., exercise), the heart needs only to pump harder is not true. Because of the high compliance of blood vessels on the venous side of the circulation and a small pressure gradient from the capillaries to the right atrium, as the heart attempts to increase blood flow by increasing stroke volume, the venous vessels collapse. This

the amount of blood returning to the heart is actually diminished, which ultimately leads to a reduction in stroke volume. For this reason, cardiac output is largely determined by the venous return or the amount of blood that returns to the heart.

## SYSTEMIC CIRCULATION

67. What is **vascular resistance**?

Vascular resistance is the force that impedes blood flow through the circulation. The resistance ( $R$ ) of an individual vessel depends directly on its length ( $l$ ) and the viscosity ( $\eta$ ) of the blood flowing through it and inversely on the radius to the fourth power ( $r^4$ ). Thus, changes in the radius of a blood vessel are the primary means by which resistance is regulated. This relationship is stated in Poiseuille's law:

$$R = \frac{\pi r^4}{8 \eta l}$$

68. Clarify the distinction between **total peripheral resistance**, **venous resistance**, and **resistance to venous return**.

~~Total peripheral resistance~~ is the complete resistance that blood encounters as it flows from the arterial (left ventricle) to the venous (right atrium) side of the circulation. ~~Venous resistance~~ is generally defined as the resistance that blood encounters as it flows from the capillaries back to the right atrium. The **resistance to venous return** is a concept that incorporates the importance of resistance, compliance, and blood volume and thus describes the dependence of blood flow in the peripheral circulation on these parameters.

69. How long are all the **blood vessels in the body**?

If all the blood vessels in the human body could be laid end-to-end, they would extend about 60,000 miles, or nearly 100,000 kilometers.

$$\frac{\Delta V}{\Delta P}$$

70. Define **compliance**.

Compliance is a term that describes the ease of stretching a vessel wall. The greater the compliance, the greater the "stretchability" of the blood vessel. Compliance is defined as a change in volume divided by a change in pressure (mL per mmHg). Thus, a highly compliant vessel will have a large change in volume for a small change in pressure. Conversely, a low compliant vessel will have a small change in volume for a large change in pressure. A highly compliant vessel is like a balloon, whereas a noncompliant or stiff vessel is like a steel tube.

71. How is **distensibility** different from **compliance**?

Distensibility and compliance are similar, but they differ in one regard. Distensibility is the compliance divided by the resting volume, so it is a normalized measure of compliance. Compliance reflects the total amount of blood stored in a given part of the circulation and is more commonly used than distensibility.

72. Can the **compliance of blood vessels** change?

Yes. The compliance, or stiffness, of blood vessels is under the control of a number of factors:

- Sympathetic nervous input
- Hormones
- Changing components of the vessel wall, such as occurs in aging

73. List factors that cause **compliance to decrease**.

- Increased sympathetic outflow
- Increased concentrations of vasoconstrictor hormones such as epinephrine and norepinephrine
- Increasing age

74. What is the relationship between the compliance of arteries and the compliance of veins?

In general, veins of the systemic circulation are 20 times more compliant than arteries. Although there is some difference in the compliance of arteries and veins as you move along the circulation at almost every level, the veins are larger and more compliant than their companion arteries.

75. List the functions of circulation.

- Delivering nutrients, vitamins, oxygen, water, and electrolytes to the tissues
- Removing products of metabolism
- Conducting hormones from one part of the body to another

76. What are the components of the systemic circulation?

Arteries	Venules
Arterioles	Veins
Capillaries	

The vessels in the circulation that transport blood at high pressure to the tissues are the arteries. Arteries have thick walls to withstand the high pressures within them. After several stages of branching and reductions in diameter, the vessels that enter into the tissues are known as arterioles. Arteriolar walls have a thick component of smooth muscle that responds to sympathetic stimulation. They therefore can act as the control valves and are the site of much of the control of blood flow in the circulation. The smallest vessels are known as capillaries, which have very thin walls. They are responsible for exchanges of fluids, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid. Capillaries are highly permeable to water, oxygen, and other substances, which can move through spaces or "pores" between adjacent capillary endothelial cells or through molecular pores in the cell membrane. After the blood has moved through the capillaries, it is collected into small vessels known as venules. Venules have some smooth muscle in their walls that can contract to increase venous resistance and decrease venous compliance, but venules are also highly compliant. Venules coalesce into progressively larger vessels known as veins, which are important for the transport of the blood back to the heart. Because so much of the blood volume resides in the veins, they are important areas for storage of blood.

77. What determines the rate of blood flow through a blood vessel?

- The pressure gradient between the two ends of the vessel
- The difficulty of the blood moving through the vessel, known as resistance

The blood flow through a vessel can be calculated based on the following equation:

$$\text{Flow} = \text{pressure gradient} \div \text{resistance}$$

For the entire circulation, the flow is equal to the cardiac output, and the pressure gradient is the arterial pressure minus the venous pressure. Resistance to blood flow is often calculated in units called peripheral resistance units (PRU). For the entire circulatory system, the resistance is 100 mmHg divided by a flow of approximately 100 mL/s or 1 PRU.

78. What is delayed compliance?

Delayed compliance is the response of the blood vessel to a sudden change in pressure. When a vessel experiences a sudden change in pressure or volume, the vascular wall slowly stretches to accommodate that increase in volume. As the vessel wall stretches, the pressure within the vessel falls, resulting in the appearance of an increase in compliance. This change in compliance over time is referred to as delayed compliance, or stress-relaxation.

79. What are the normal levels of arterial and venous pressure in the body?

The pressure in the arteries is highly pulsatile. The peak pressure, known as systolic pressure, is approximately 120 mmHg. The trough pressure, known as diastolic pressure, is approximately 80 mmHg. The difference between the systolic and diastolic pressure is known as the pulse pressure.



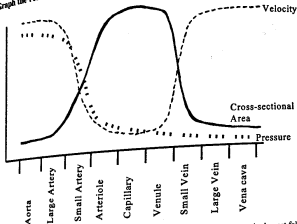
**pulse pressure.** The pulse pressure depends on the amount of blood pumped by the heart on each beat, or the stroke volume, and the compliance of the arteriole tree. As the compliance of the arteries decreases, such as occurs during aging, the pulse pressure will increase.

Venous pressures are much lower than arterial pressure, ranging from about 15 mmHg systemic pressure in the venules just after the capillaries to approximately 0 mmHg as the veins drain into the right atrium.

**88. How is the blood volume distributed throughout the circulation?**

The vast majority of the blood is in the compliant venous circulation, with nearly 1000 mL or 1 L in the largest veins (the vena cava), and approximately the same amount in the venous branches, including the venules and the terminal veins. Although the number of capillaries is high, their individual volumes are small, so the total blood volume in the capillaries is approximately 300 mL. Similarly, the small size and low compliance of the arteries results in only about 1 L of volume being on the arterial side of the circulation.

**89. Graph the relative pressure, velocity, and cross-sectional area of the circulation.**



relative pressure, velocity, and cross-sectional area of the circulation demonstrating the largest fall in pressure at the small arteries and arterioles, as well as the large area and low velocity in the microcirculation.

**90. How does gravity influence the blood volume distribution in an upright person?**

Because of the weight of the column of blood in an upright human and the high compliance of the veins, blood tends to accumulate in the lower extremities. Several mechanisms facilitate the return of blood from the extremities to the heart:

- Venous valves
- Contraction of skeletal muscle
- Autonomic reflexes, which influence venous tone
- Valves, which are found in the larger veins, allow blood to move only toward the heart. The presence of these valves, combined with the squeezing of blood vessels by contracting skeletal muscle, create what is known as the **skeletal muscle blood pump**. This combination of a vascular and an extravascular system results in active pumping of blood from the periphery back to the heart.

83. The words *venodilation*, *vasodilation*, *arterial dilation*, and *venous dilation* are often used interchangeably. What does each mean?

- **Venodilation** and **venous dilation**—an increase in the size of veins
- **Vasodilation**—an increase in the size of either arterioles or veins
- **Arterial dilation**—an increase in the diameter of arterioles

For constriction, we refer to arterial constrictions for arteries, venoconstriction for veins, and vasoconstriction for both.

### REGULATION OF CARDIAC OUTPUT AND VENOUS RETURN

84. What is the normal value for cardiac output in a human?

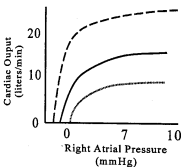
Cardiac output is highly variable, depending on the metabolic demands of the organs and tissues of the body. At rest, cardiac output is approximately 5 L/min in a 70-kg person.

85. What happens to cardiac output when the body's need for oxygen increases?

As the needs of the body increase, for example, during exercise, the amount of blood pumped by the heart increases. This increase in blood flow is exactly proportional to the increased demand for oxygen by the tissues.

86. How do the systemic circulation and the heart receive signals to circulate more blood when needed?

There are several mechanisms by which cardiac output can be increased as metabolism is increased. Sympathetic outflow to the heart can increase both heart rate and contractility, leading to an increase in cardiac output (see figure). However, this alone does not increase cardiac output effectively. Dilatation of the systemic circulation as a result of functional hyperemia or autoregulation increases venous return and thus increases cardiac output.



Family of cardiac function curves showing normal (solid), increased (dashed), and decreased (dotted) levels of sympathetic outflow to the heart. Contractility of the heart is proportional to the slope of the cardiac function curve.

87. What is functional hyperemia (active hyperemia)?

Active hyperemia is the increase in blood flow due to an increase in the rate of metabolism of the tissue fed by a given blood supply. As the metabolism of tissue increases, the requirements for oxygen and other substrates are increased. These requirements are met by increases in blood flow that are precisely matched to the increased metabolic demand of the tissue.

88. Contrast active hyperemia and reactive hyperemia.

Although active hyperemia and reactive hyperemia are similar in some respects, reactive hyperemia is the excess blood flow that occurs after a period in which the tissues are not supplied with the appropriate blood flow to meet metabolic needs. After a period in which blood flow has been occluded, for example, by a tourniquet, release of the occlusion results in a blood flow that

is greater than that which occurred before the occlusion. The magnitude of the increase in blood flow after the occlusion is proportional to the duration of the period in which the flow was inadequate. This increase in flow above control is sometimes said to be "paying back the oxygen debt" acquired during the period of occlusion.

**89. What is blood flow autoregulation?**  
Autoregulation is the mechanisms by which tissue regulates its own blood supply. For example, when blood pressure is reduced, blood flow tends to fall. This decrease in blood flow is resisted by dilation of arterioles throughout the body. This dilation reduces the resistance to blood flow, thus restoring the delivery of blood to the tissues. Autoregulation is generally divided into the **metabolic response** and the **myogenic response**.

**90. Compare the metabolic and myogenic responses in the local control of the circulation.**  
The myogenic response is a property of a blood vessel resulting in active constriction as pressure rises and in dilation as pressure falls in an effort to maintain a given flow rate. This property originates within the vessel wall and thus does not require interaction with the tissue that the vessel feeds. The metabolic response, which causes constriction as flow increases and dilation as flow falls, arises from the production and washout of dilator metabolites by the tissue. When flow is too low, products of tissue metabolism that are normally washed away build up in the tissue and cause vessels to dilate. When flow is too high, the dilator metabolite concentrations are reduced, resulting in vessel constriction. Under normal conditions, the metabolic and myogenic responses work together to maintain tissue blood flow constant.

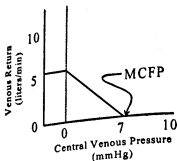
**91. How do extrinsic control mechanisms of vascular resistance and intrinsic controllers, such as functional hyperemia and the myogenic response, relate to one another?**  
Extrinsic control of vascular resistance (such as the sympathetic nerves and vasoactive hormones) is superimposed on intrinsic autoregulation. This becomes important in many situations when cardiac output must be **shunted** toward one region or another for the preservation of the organism. An example of this is one that occurs with exercise. At the onset of exercise, there is an increase in sympathetic activity that causes a peripheral arterial vasoconstriction, leading to an increase in peripheral resistance that increases blood pressure. However, because of accumulation of metabolites in exercising muscle, blood flow to these sites is increased due to the local metabolic vasodilatory response.

**92. How much do tissues (organs) rely on autoregulation versus extrinsic control mechanisms?**  
Some organs depend primarily on autoregulation to control blood flow, whereas other tissues are primarily regulated by extrinsic (neural) mechanisms. In general, organs that are thought to be immediately critical to sustain life utilize autoregulation to a greater degree. These include the (brain, kidney, and heart). Conversely, the cutaneous circulation is regulated primarily by the level of sympathetic vasoconstrictor tone to its vessels. Many tissues utilize both autoregulation and sympathetic neural control, depending on circumstances. For example, skeletal muscle circulation is generally under sympathetic neural control, but this control can be overridden during times of increased metabolic demand by the tissues, such as exercise. Increased sympathetic stimulation of the splanchnic circulation can greatly reduce blood flow through this tissue and release stored blood volume, but over a period of time, the accumulation of metabolites will override the extrinsic neural regulation, and flow will be restored to meet the demands of the tissue.

**93. If the amount of blood that flows through the body is regulated by the venous return, then what is it that controls the venous return?**

The venous return, or the amount of blood that comes back to the heart, is determined by the following:

- Blood volume
- Compliance of the arteries and veins
- Resistance of the arteries and veins



The venous return curve describes the relationship between central venous pressure and venous return. The inverse slope of the curve is the resistance to venous return.

Because vessels are distensible and the heart is preload-sensitive, we can define a relationship that includes Poiseuille's law but also extends it. This relationship is known as the **venous return relationship** (see figure).

To understand the venous return relationship, we must first understand a concept called the **mean circulatory filling pressure (MCFP)**, which is defined as the sum of the volume in the arteries + the volume in the veins  $\div$  the total compliance of the circulation. The MCFP is indicative of the fullness of the circulation. MCFP also represents the pressure that drives blood back to the heart. Therefore, the pressure gradient for venous return is  $\text{MCFP} - \text{right atrial pressure}$ . Because flow = the pressure gradient  $\div$  the resistance across that gradient, the resistance to venous return (RVR) is defined as the pressure gradient ( $\text{MCFP} - \text{right atrial pressure}$ )  $\div$  the venous return. This resistance to venous return is not the same as total peripheral resistance because it takes into account the venous resistance ( $R_V$ ), the arterial resistance ( $R_A$ ), and the compliance of the circulation:

$$\text{RVR} = \frac{R_V + R_A}{20}$$

Clearly the venous return is equal to  $\text{MCFP} - \text{the right atrial pressure} \div \text{the resistance to venous return}$ . Thus, venous return is regulated by regulation of the MCFP (the fullness of the circulation) and the resistance to venous return (arterial resistance, venous resistance, and compliance).

#### 94. What are the factors that alter the MCFP?

- Changes in blood volume
- Changes in arterial compliance
- Changes in venous compliance

Changes in vascular resistance do not affect the mean circulatory filling pressure.

#### 95. What factors change the resistance to venous return?

The resistance to venous return is determined primarily by constriction or dilation of arteries and veins. Increasing the resistance of the arteries or the resistance of the veins increases the resistance to venous return and therefore decreases the amount of blood returning to the heart. Because resistance of the arterioles can be controlled by local factors, changing the resistance to venous return provides a mechanism by which the needs of the tissues may be met with an increased blood flow.

#### 96. How do vasoconstrictor hormones affect venous return?

Hormones such as norepinephrine, epinephrine, angiotensin, and vasopressin increase both the MCFP and the resistance to venous return. Conversely, hormones such as acetylcholine and drugs such as sodium nitroprusside decrease the MCFP and the resistance to venous return.

97. What do increases in sympathetic nerve activity do to MCFP and resistance to venous return?

- Increase MCFP
- Increase resistance to venous return

98. What is the normal level of MCFP? MCFP, or the pressure that occurs in the circulation when the flow is equal to 0, is approximately 7 mmHg under normal conditions.

99. What factors can cause increases in the level of MCFP?

- Increases in blood volume
- Increases in sympathetic tone
- Increases in levels of circulating constrictor hormones

100. What is the maximal increase in the level of MCFP?  
20 mmHg.

101. What factors may cause decreases in the level of MCFP?

- Hemorrhage
- Reductions of sympathetic outflow
- Vasodilators

102. What is the minimal level of MCFP?  
4mmHg.

## REGULATION OF BLOOD PRESSURE

103. What is the normal value of ~~blood pressure~~?

Approximately 120 mmHg for systolic and 80 mmHg for diastolic. This may be quite variable, however. Normal blood pressures in infants may be as low as 90 over 40, and blood pressure tends to increase throughout life. In addition, over a 24-hour period, blood pressure may be somewhat variable, with lower values occurring during sleep and higher values occurring during waking cycles. In most people, the daily average of the mean arterial pressure is normally regulated at about 100 mmHg, with fluctuations of approximately  $\pm 20$  mmHg. Despite these fluctuations, blood pressure is fairly stable over life and is well regulated on a moment-to-moment basis, a daily basis, and over the entire life span.

104. Why is regulation of ~~mean arterial pressure needed~~?

- To provide the organs with blood flow at a constant perfusion pressure so that each organ system can alter its resistance to achieve the desired flow during altered metabolic needs, hydrostatic destabilization, and alter blood volume states
- To optimize the cardiovascular work and minimize cardiac, vascular, and renal damage

105. How is ~~mean arterial pressure regulated~~?

The basic scheme by which blood pressure is regulated is through a feedback control system consisting of pressure sensors and effector mechanisms that can alter the blood pressure. If pressure becomes altered, such as might occur during hemorrhage, a sensor, or **baroreceptor**, senses the reduction in pressure and activates an effector mechanism to return blood pressure toward its **set point**. This response is termed **negative feedback control**. The degree of effectiveness with which a control system maintains constant conditions (homeostasis) is determined by the gain of the negative feedback. Nearly all body control systems are operated by negative feedback. The primary reflex that helps to control blood pressure on a beat-to-beat basis is the **baroreceptor reflex**.

106. What types of effector mechanisms are important for the regulation of blood pressure?

**Extrinsic mechanisms:**

Sympathetic nervous system  
Parasympathetic nervous system

**Intrinsic mechanisms:**

Myogenic response  
Metabolic response

**Hormonal controllers:**

Renin-angiotensin system  
Vasopressin  
Atrial natriuretic peptide  
Kallikrein-kinin system  
Kallikrein-kinin system

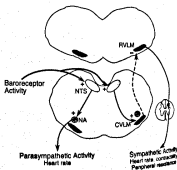
107. How does the sympathetic nervous system act as an effector in blood pressure control?

Sympathetic neurons from the rostral ventrolateral medulla (RVLM) descend through the spinal cord in the bulbospinal pathway and synapse on preganglionic neuronal cell bodies in the intermediolateral cell column. Preganglionic sympathetic fibers exit the thoracic and lumbar spinal cord and activate postganglionic nerve cells in ganglia located throughout the body. The postganglionic sympathetic fibers terminate as sympathetic fibers on arterioles, venules, and the heart. These fibers, through release of the neurotransmitter norepinephrine, cause a tonic sympathetic vasoconstriction of arteries and veins and can accelerate heart rate. The tonic constriction of blood vessels is sometimes referred to as **vasomotor** or **vascular tone**. Vasomotor tone keeps vessels partly constricted so that they can both dilate and constrict around this level of **resting tone**.

108. How does the baroreceptor reflex control blood pressure?

Two sites in the cardiovascular system contain baroreceptors, fine nerve endings that are activated by stretch of the vessel walls in which they lie: the carotid sinus and the aortic arch. These pressure-sensitive receptors send afferent nerve activity through the ninth and tenth cranial nerves, respectively, to the **nucleus of the tractus solitarius (NTS)**, which activates neurons that serve as the first relay site of the baroreflex. These NTS neurons then activate neurons in the **caudal ventrolateral medulla (CVLM)**, which in turn inhibit the neurons in the rostral ventrolateral medulla, which normally excite sympathetic preganglionic neurons in the spinal cord. Thus, activation of the baroreceptors by increases in pressure, or increased stretch of the vessel walls, results in a decrease in sympathetic activity. This decrease in sympathetic activity reduces the vasomotor tone, causing dilation of the blood vessels, and slows heart rate, both of which help to lower blood pressure back to normal. In addition to decreasing sympathetic activity, activation of the baroreceptors increases parasympathetic nerve activity. Neurons in the NTS that are activated by baroreceptor afferent activity also innervate neurons in the **nucleus ambiguus (NA)** in the medulla, which are the preganglionic parasympathetic nerve cell bodies that have fibers in the vagus nerve. These neurons innervate postganglionic neurons contained in ganglia near the heart. Thus, when the baroreceptors are activated, there is an increase in parasympathetic nerve activ-

Diagram of the baroreceptor reflex pathway in the medulla. Baroreceptor afferent activity first synapses on neurons in the nucleus tractus solitarius (NTS). These neurons activate other neurons in either the nucleus ambiguus (NA) or caudal ventrolateral medulla (CVLM). Neurons in the NA are cell bodies for preganglionic nerve fibers that innervate the heart. Thus, increases in baroreceptor activity will increase parasympathetic drive to the heart. Neurons in the CVLM inhibit neurons in the RVLM, which activate cell bodies of preganglionic sympathetic nerve fibers in the spinal cord. Thus, increases in baroreceptor activity will decrease sympathetic drive to the heart and blood vessels. The net effect of increases in baroreceptor activity is a decrease in heart rate and peripheral resistance.



ity to the heart, which helps to slow heart rate. If blood pressure decreases, the level of baroreceptor activation decreases, and thus there is less excitation of neurons in the NTS. This results in less inhibition of sympathetic activity and less activation of parasympathetic activity. This results in increases in vasomotor tone and heart rate, which help to elevate blood pressure back to normal. Note that the sympathetic and parasympathetic nervous systems act reciprocally to control blood pressure, so that increases in one are accompanied by decreases in the other.

The baroreceptor reflex is highly effective at rapidly controlling blood pressure during short-term perturbations, such as postural changes. One important feature of this control mechanism is that it is rapidly adapting so that it is capable of normalizing blood pressure even if the long-term level of blood pressure is changed.

108. Are there other types of sensors that are important in the regulation of blood pressure?

Yes. Another important neural control mechanism involved in blood pressure control is peripheral chemoreceptors. Chemoreceptors are located primarily in carotid and aortic bodies. They are stimulated by low arterial  $PO_2$  but also may be stimulated by arterial pressures that fall below approximately 60 mmHg. Stimulation of chemoreceptors leads to an increased sympathetic tone (vasoconstriction) and increased vagal tone (bradycardia). In addition, there are mechanoreceptors in the heart, primarily the left ventricle, that act much like baroreceptors and can contribute to regulation of pressure, although the gain of this reflex is much less than that of the arterial baroreceptors.

111. Summarize the nervous control of arterial pressure.

Nervous control of arterial pressure is accomplished primarily by baroreceptors, peripheral chemoreceptors, cardiac mechanoreceptors, and central nervous system ischemic response. It acts through changes of sympathetic and vagal tone (control of total peripheral resistance, MCFP, and alterations in cardiac function). Nervous control of the circulation acts quickly; however, these systems tend to adapt when exposed to extended periods of blood pressure changes.

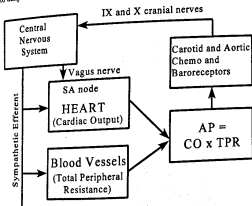


Diagram of the neural control of the circulation. IX = Glossopharyngeal nerve; X = vagus nerve; AP = arterial pressure; CO = cardiac output; TPR = total peripheral resistance.

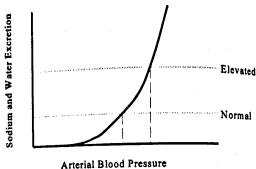
111. If neural control systems are rapidly adapting, what are the mechanisms that are responsible for the long-term regulation of blood pressure?

Increases in blood volume cause increases in blood pressure by acting through cardiac output. Because blood volume is controlled primarily by renal excretory mechanisms, the kidney is

the primary long-term controller of blood pressure in the body. The regulation of blood pressure by the kidney is referred to as the **pressure diuresis theory**.

### 112. What is the pressure diuresis theory?

The ability of the kidney to excrete sodium and water depends directly on the arterial pressure. As arterial pressure rises, urinary sodium and volume output increases (see figure), which results in a decrease in blood volume. This decrease in blood volume causes a reduction in cardiac output and therefore a reduction in blood pressure. As blood pressure is reduced, the excretory ability of the kidney is also reduced, restoring a steady state. The consequence of the pressure diuresis theory is that long-term blood pressure is controlled by the renal excretory ability, and the total peripheral resistance determines blood pressure only in the short term. Most importantly, this theory says that changes in renal vascular resistance or renal filtration and reabsorption are the only ways to alter blood pressure in the long term.



The relationship of renal perfusion pressure and sodium or water excretion. Dotted lines show normal or elevated sodium intake. Dashed lines show the resulting arterial blood pressure. The slope of this curve can be modified by angiotensin, aldosterone, and other factors.

### 113. What is the autoregulatory multiplier effect of total peripheral resistance?

Small increases in blood volume and cardiac output can have large effects on systemic vascular resistance (i.e., arterial or vasoconstriction) because increases in extracellular fluid volume and blood volume increase MCFP, which increases both venous return and cardiac output. Increases in cardiac output, acting through autoregulatory mechanisms, increase total peripheral resistance. Because arterial pressure equals cardiac output times total peripheral resistance, and because both cardiac output and total peripheral resistance are increased by increasing blood volume, the resulting increase in arterial pressure is referred to as a **multiplied effect**.

## MICROCIRCULATION

### 114. What is the microcirculation?

The microcirculation is made up of the smallest blood vessels. It is generally defined as including the vessels with diameters less than 200  $\mu$ . These are the vessels that penetrate into the parenchymal tissue and are responsible for the primary control of blood pressure and fluid or change in the circulation. The smallest vessels in the microcirculation are referred to as the **terminal microcirculation**. These are arterioles with diameters less than 100  $\mu$ , capillaries with diameters between 4 and 8  $\mu$ , and venules with diameters less than 150  $\mu$ .



115. What is the primary function of the microcirculation?

The microcirculation is responsible for exchange of nutrients, metabolites, oxygen,  $\text{CO}_2$ , ions, water, and heat. The exchange of materials between the circulatory system and the cells of the body takes place mainly in the capillaries. These vessels are small, averaging only 4–8  $\mu$  in diameter. The average capillary is approximately 500  $\mu$  in length.

116. How do substances move across the capillary wall?

- Transcellular—pathway for lipophilic substances
- Clefts—pathway for hydrophilic substances
- Fenestrate—pathway for large proteins
- Pinocytotic vessels—pathway for large hydrophilic molecules

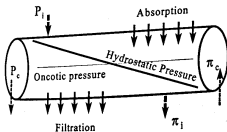
117. Name the forces involved in the movement of water across the capillary wall.

The Starling forces:

- Hydrostatic pressure inside the capillary
- Hydrostatic pressure of the interstitial fluid
- Colloid osmotic pressure of the plasma
- Interstitial fluid colloid osmotic pressure

118. Explain how the Starling forces work.

The balance between hydrostatic (pressure) and osmotic forces determines the net movement of water from the capillary to the interstitial space. Colloid osmotic pressure is the pressure that occurs because of the presence of impermeable proteins in the plasma and interstitial fluid. The capillary membrane is nearly impermeable to protein. When the protein concentration is high on one side of the capillary membrane and low on the other, water moves in an attempt to equalize the concentrations. This pulling force on the water is colloid osmotic pressure. Most ions do not contribute to the forces across the capillary membrane because the membrane is freely permeable to them and they are in equilibrium. Under normal conditions, the balance of forces favors a net movement of water from the capillary to the interstitium. Nearly all of the fluid that enters the interstitial space is absorbed by lymphatic capillaries and moves into collecting lymphatics and into lymph vessels, where it is finally returned for blood circulation. Thus, interstitial fluid volume is the balance between capillary fluid filtration and lymphatic drainage.



Schematic representation of the Starling forces acting on the capillary.  $P_c$  = capillary hydrostatic pressure;  $P_i$  = interstitial fluid pressure;  $\pi_c$  = capillary colloid osmotic pressure;  $\pi_i$  = interstitial fluid colloid osmotic pressure. Dashed arrows show direction in which force acts. Solid arrows show direction of fluid movement.

119. How are endothelial cells in a microcirculation involved in regulation of blood pressure?

Endothelial cells lining blood vessels experience deformational forces because of the velocity of blood flow and the viscosity of the blood. These endothelial cells in vascular beds, ranging

from large muscular arteries to microvascular capillaries of specific organ systems, are capable of releasing mediators, which activate adjacent cell types. Responses of these cells depend on their differential recognition of the mediator signals and the functions coupled to a biochemical transduction system. For example, physical forces, hormones, cytokines, and coagulation products, which act on endothelial cells, can cause relaxation, contraction, proliferation, or chemotaxis in adjacent smooth muscle cells. Smooth muscle cells are not the only responder cells involved in endothelial responses; virtually all parenchymal cells can respond to mediators released by endothelial cells.

**120. What type of vasoactive substances are released from endothelial cells?**

**Proteins**

Thrombin

**Peptides**

Substance P

Vasopressin

Angiotensin

**Kinins**

Bradykinin

**Amines**

Serotonin

Nucleotides

Adenosine triphosphate (ATP)

Adenosine diphosphate (ADP)

**Metabolites of arachidonic acid**

Leukotrienes

Prostaglandins

**Hydroxy-eicosatetraenoic acids (HETEs)**

ETEs

Nitric oxide

**121. Describe the action of nitric oxide.**

Nitric oxide is released from endothelial cells and causes a potent relaxation of vascular smooth muscle. When blood flow in the microcirculatory vessels is increased, shear forces acting on the endothelial cells cause the release of nitric oxide, which dilates the blood vessels. The flow-dependent dilation is an important regulator of shear stress and may be part of the mechanism by which flow is regulated during functional hyperemia.

### SPECIAL CIRCULATIONS

**122. What is the splanchnic circulation?**

The splanchnic circulation is the blood supply to the liver, spleen, pancreas, stomach, and intestines. It is here that nutrients are absorbed from the gastrointestinal tract and enter the bloodstream. Major hemodynamic characteristics of this circulation are its large volume and high compliance.

**123. What proportion of the cardiac output does the liver receive?**

The liver receives about 25% of the cardiac output, or about 1250 mL/min. Of this total, approximately three-fourths comes from the portal vein, and about one-fourth comes from the hepatic artery. Portal venous blood reaches the liver from the intestinal circulation, where it has absorbed nutrients from the intestinal villi. Hepatic arterial blood is rich in oxygen and supplies the nutritive needs of the hepatic cells. A constant oxygen consumption in the liver is maintained by a variable and efficient extraction of oxygen by the hepatocytes.

**124. What are the pressures in the hepatic circulation?**

Portal venous pressure is about 10 mmHg, whereas the hepatic arterial pressure is about 90 mmHg. Because the resistance of the upstream vessels is much higher than the downstream vessels, the pressure in the sinusoids is quite low, only about 2–3 mmHg. The portal venous circulation is not autoregulated.

**125. How does the liver contribute to the overall hemodynamics of the body?**

The hepatic circulation is highly compliant. Because of this compliance and the large size of the organ, the liver serves as an important storage reservoir for blood. The liver normally contains approximately 15% of the total blood volume, which can be mobilized by increased sympathetic nerve activity in situations such as hemorrhage. In situations in which venous pressures are increased, large volumes of blood may be translocated to the liver, causing it to become enlarged.

**126. What are the major characteristics of the intestinal circulation?**

The vessels of the intestinal circulation are responsive to changes in sympathetic nerve activity as well as to circulating hormones. Both the resistance and the compliance of the intestinal circulation are under important sympathetic control. The intestinal circulation is highly compliant, so increased blood flow and volume in this vascular bed may cause reductions of blood flow to other organs. Because of the anatomic arrangement of the circulation in the intestinal villus, a countercurrent exchanger exists. This countercurrent blood flow may cause the tip of the villus to become ischemic during periods of low blood flow.

**127. What is the blood flow to skeletal muscle?**

Skeletal muscle blood flow is highly variable, depending directly on the metabolic activity of the tissue. At rest, intermittent contractions and relaxations of small arterioles cause a large percentage of the muscle capillary bed to be nonperfused at any given time. As a result, resting muscle has a low blood flow (approximately 2–3 mL/min/100 g). During exercise, arterioles within the muscle relax, and blood flow can increase dramatically (up to 100 mL/min/100 g in some muscles).

**128. How is skeletal muscle blood flow controlled?**

At rest, skeletal muscle blood flow is regulated by an interplay of extrinsic (sympathetic nerve activity) and local (metabolic) effects with the sympathetic effects dominating. During active muscle contraction, the local release of vasodilator metabolites, thought to include potassium,  $\text{CO}_2$ , lactic acid, or pH, provides the major control, completely overriding the sympathetic neural effects (functional hyperemia). The contraction of the muscle itself also plays a role in blood flow regulation in skeletal muscle, with maximal flow occurring during the periods between muscle contractions when the vessels are not being compressed by the muscle fibers.

**129. What is unique about the cerebral circulation?**

A constant blood supply to the brain is critical because even brief periods of ischemia can cause irreversible tissue damage. This constant blood flow is supported by an anatomic vascular pattern comprising many anastomoses, or alternative pathways for blood flow in the brain and strong local control of resistance. On a moment-to-moment basis, blood flow in the brain is maintained by this local autoregulation and under some extreme conditions by initiating powerful reflexes to maintain arterial blood pressure. Generally, total cerebral blood flow is maintained constant with blood being shunted to areas of high metabolic activity. For example, activation of visual cortex by a flashing light pattern on the retina increases blood flow only to areas associated with vision and not to other cortical areas.

**130. How is cerebral blood flow regulated?**

Cerebral blood flow is regulated almost exclusively by metabolic factors such as  $\text{CO}_2$ ,  $\text{K}^+$ , and adenosine. Although cerebral blood vessels are innervated by sympathetic nerve fibers, their role in the control of blood flow is not clear.

### 131. What is the blood-brain barrier?

The capillaries of the cerebral circulation are significantly less permeable to proteins, peptides, and ions than capillaries in other areas of the body. This barrier to the movement of substances from the blood to the brain parenchyma protects the neurons from effects of substances being transported in the blood and is referred to as the **blood-brain barrier**. Anatomically, the blood-brain barrier results primarily from tight junctions between the endothelial cells of the cerebral capillaries.

### 132. What is the main function of the skin circulation?

In addition to supplying nutrients to the tissue, the skin circulation aids in the regulation of body temperature. When the body temperature is elevated, these vessels dilate to deliver more blood to the body surface, where it can be cooled. Under extreme conditions when heat must be conserved, skin blood vessels constrict, resulting in a nearly complete cessation of skin blood flow.

### 133. How is the skin blood flow controlled?

Blood flow to the skin is the most variable in the body. Skin blood vessels dilate directly in response to heat and constrict in response to cold. Most of the control occurs by sympathetic nerve activity evoked by neurons involved in temperature regulation. Blood flow to the skin can account for up to 25% of the cardiac output when body temperature is markedly elevated.

### 134. What are the factors that influence the blood flow to the heart?

- Physical factors
- Neural and neurohumoral factors
- Metabolic factors

The **physical factors** include maintenance of blood pressure and the squeezing of the blood vessels during cardiac contraction. In contrast with other organs, the heart is responsible for maintaining arterial pressure. Because of this, decreases in cardiac function may be amplified by resulting falls in coronary artery perfusion pressure, which result in reductions in coronary blood flow and even further reductions in cardiac function due to cardiac ischemia. Most of the perfusion of the heart occurs during diastole because this is the period when the cardiac muscle relaxes, allowing passage of blood through the vessels. During systole, the contraction of the ventricles causes extravascular compression, which can completely stop blood flow through the coronary vasculature.

### 135. What is the most important regulator of coronary blood flow?

The coronary circulation supplies the metabolic needs of the cardiac tissue. One of the most striking characteristics of the coronary circulation is the tight coupling between blood flow and metabolic activity. Thus, **metabolic autoregulation** and **functional hyperemia** play the most important role in the regulation of coronary perfusion. The mechanism for this link between cardiac metabolic rate and coronary blood flow is still not completely understood. What is known is that a decrease in the ratio of oxygen supply to oxygen demand causes the release of a potent vasodilator substance into the interstitial fluid of the heart, where it can relax coronary blood vessels in an attempt to normalize blood flow.

### 136. How important is the neural regulation of coronary blood flow?

Neural regulation of coronary blood flow is much less important than the metabolic regulation. Activation of cardiac sympathetic nerves, which increase heart rate and contractility, causes an increased rate of coronary metabolism and thus acts indirectly to increase blood flow.

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