I. CIRCUITRY OF THE CARDIOVASCULAR SYSTEM (FIGURE 3-1)

A. Cardiac output of the left heart equals cardiac output of the right heart.
   - Cardiac output from the left side of the heart is the systemic blood flow.
   - Cardiac output from the right side of the heart is the pulmonary blood flow.

B. Direction of blood flow
   - Blood flows along the following course:
     1. From the lungs to the left atrium via the pulmonary vein
     2. From the left atrium to the left ventricle through the mitral valve
     3. From the left ventricle to the aorta through the aortic valve
     4. From the aorta to the systemic arteries and the systemic tissues (i.e., cerebral, coronary, renal, splanchnic, skeletal muscle, and skin)
     5. From the tissues to the systemic veins and vena cava
     6. From the vena cava (mixed venous blood) to the right atrium
     7. From the right atrium to the right ventricle through the tricuspid valve
     8. From the right ventricle to the pulmonary artery through the pulmonic valve
     9. From the pulmonary artery to the lungs for oxygenation

II. HEMODYNAMICS

A. Components of the vasculature
   1. Arteries
      - deliver oxygenated blood to the tissues.
      - are thick-walled, with extensive elastic tissue and smooth muscle.
      - are under high pressure.
      - The blood volume contained in the arteries is called the stressed volume.
   2. Arterioles
      - are the smallest branches of the arteries.
      - are the site of highest resistance in the cardiovascular system.
      - have a smooth muscle wall that is extensively innervated by autonomic nerve fibers.
      - Arteriolar resistance is regulated by the autonomic nervous system (ANS).
      - $\alpha_1$-Adrenergic receptors are found on the arterioles of the skin, splanchnic, and renal circulations.
      - $\beta_2$-Adrenergic receptors are found on arterioles of skeletal muscle.
3. Capillaries
- have the largest total cross-sectional and surface area.
- consist of a single layer of endothelial cells surrounded by basal lamina.
- are thin-walled.
- are the site of exchange of nutrients, water, and gases.

4. Venules
- are formed from merged capillaries.

5. Veins
- progressively merge to form larger veins. The largest vein, the vena cava, returns blood to the heart.
- are thin-walled.
- are under low pressure.
- contain the highest proportion of the blood in the cardiovascular system.
- The blood volume contained in the veins is called the unstressed volume.
- have α₁-adrenergic receptors.

B. Velocity of blood flow
- can be expressed by the following equation:

\[ v = \frac{Q}{A} \]

where:
- \( v \) = velocity (cm/sec)
- \( Q \) = blood flow (mL/min)
- \( A \) = cross-sectional area (cm²)

- Velocity is directly proportional to blood flow and inversely proportional to the cross-sectional area at any level of the cardiovascular system.
For example, blood velocity is higher in the aorta (small cross-sectional area) than in the sum of all of the capillaries (large cross-sectional area). The lower velocity of blood in the capillaries optimizes conditions for exchange of substances across the capillary wall.

C. Blood flow

- Blood flow can be expressed by the following equation:

$$Q = \frac{\Delta P}{R}$$

or

$$\text{Cardiac output} = \frac{\text{Mean arterial pressure} - \text{Right atrial pressure}}{\text{Total peripheral resistance (TPR)}}$$

where:

- $Q$ = flow or cardiac output (mL/min)
- $\Delta P$ = pressure gradient (mm Hg)
- $R$ = resistance or total peripheral resistance (mm Hg/mL/min)

- The equation for blood flow (or cardiac output) is analogous to Ohm’s law for electrical circuits ($I = V/R$), where flow is analogous to current, and pressure is analogous to voltage.
- The pressure gradient ($\Delta P$) drives blood flow.
- Thus, blood flows from high pressure to low pressure.
- Blood flow is inversely proportional to the resistance of the blood vessels.

D. Resistance

- Poiseuille’s equation gives factors that change the resistance of blood vessels.

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

where:

- $R$ = resistance
- $\eta$ = viscosity of blood
- $l$ = length of blood vessel
- $r^4$ = radius of blood vessel to the fourth power

- Resistance is directly proportional to the viscosity of the blood. For example, increasing viscosity by increasing hematocrit will increase resistance and decrease blood flow.
- Resistance is directly proportional to the length of the vessel.
- Resistance is inversely proportional to the fourth power of the vessel radius. This relationship is powerful. For example, if blood vessel radius decreases by a factor of 2, then resistance increases by a factor of 16 ($2^4$), and blood flow accordingly decreases by a factor of 16.

1. Resistances in parallel or series

a. Parallel resistance is illustrated by the systemic circulation. Each organ is supplied by an artery that branches off the aorta. The total resistance of this parallel arrangement is expressed by the following equation:

$$\frac{1}{R_{\text{total}}} = \frac{1}{R_a} + \frac{1}{R_b} + \cdots + \frac{1}{R_n}$$

$R_a$, $R_b$, and $R_n$ are the resistances of the renal, hepatic, and other arteries, respectively.

- Each artery in parallel receives a fraction of the total blood flow.
- The total resistance is less than the resistance of any of the individual arteries.
- When an artery is added in parallel, the total resistance decreases.
- In each parallel artery, the pressure is the same.

b. Series resistance is illustrated by the arrangement of blood vessels within a given organ. Each organ is supplied by a large artery, smaller arteries, arterioles, capillaries,
and veins arranged in series. The total resistance is the sum of the individual resistances, as expressed by the following equation:

\[ R_{\text{total}} = R_{\text{artery}} + R_{\text{arterioles}} + R_{\text{capillaries}} \]

- The largest proportion of resistance in this series is contributed by the arterioles.
- Each blood vessel (e.g., the largest artery) or set of blood vessels (e.g., all of the capillaries) in series receive the same total blood flow. Thus, blood flow through the largest artery is the same as the total blood flow through all of the capillaries.
- As blood flows through the series of blood vessels, the pressure decreases.

2. Laminar flow versus turbulent flow

- Laminar flow is streamlined (in a straight line); turbulent flow is not.
- Reynolds number predicts whether blood flow will be laminar or turbulent.
- When Reynolds number is increased, there is a greater tendency for turbulence, which causes audible vibrations called bruits. Reynolds number (and therefore turbulence) is increased by the following factors:
  a. ↓ blood viscosity (e.g., ↓ hematocrit, anemia)
  b. ↑ blood velocity (e.g., narrowing of a vessel)

3. Shear

- Is a consequence of the fact that blood travels at different velocities within a blood vessel.
- Velocity of blood is zero at the wall and highest at the center of the vessel.
- Shear is therefore highest at the wall, where the difference in blood velocity is greatest and lowest at the center of the vessel, where blood velocity is constant.

E. Capacitance (compliance)

- describes the distensibility of blood vessels.
- is inversely related to elastance, or stiffness. The greater the amount of elastic tissue there is in a blood vessel, the higher the elastance is, and the lower the compliance is.
- is expressed by the following equation:

\[ C = \frac{V}{P} \]

\[ \text{where:} \]
\[ C = \text{capacitance, or compliance (mL/mm Hg)} \]
\[ V = \text{volume (mL)} \]
\[ P = \text{pressure (mm Hg)} \]

- is directly proportional to volume and inversely proportional to pressure.
- describes how volume changes in response to a change in pressure.
- is much greater for veins than for arteries. As a result, more blood volume is contained in the veins (unstressed volume) than in the arteries (stressed volume).
- Changes in the capacitance of the veins produce changes in unstressed volume. For example, a decrease in venous capacitance decreases unstressed volume and increases stressed volume by shifting blood from the veins to the arteries.
- Capacitance of the arteries decreases with age; as a person ages, the arteries become stiffer and less distensible.

F. Pressure profile in blood vessels

- As blood flows through the systemic circulation, pressure decreases progressively because of the resistance to blood flow.
- Thus, pressure is highest in the aorta and large arteries and lowest in the vena cavae.
The largest decrease in pressure occurs across the arterioles because they are the site of highest resistance. Mean pressures in the systemic circulation are as follows:

1. Aorta, 100 mm Hg
2. Arterioles, 50 mm Hg
3. Capillaries, 20 mm Hg
4. Vena cava, 4 mm Hg

G. Arterial pressure (Figure 3-2)

- is pulsatile.
- is not constant during a cardiac cycle.

1. Systolic pressure
   - is the highest arterial pressure during a cardiac cycle.
   - is measured after the heart contracts (systole) and blood is ejected into the arterial system.

2. Diastolic pressure
   - is the lowest arterial pressure during a cardiac cycle.
   - is measured when the heart is relaxed (diastole) and blood is returned to the heart via the veins.

3. Pulse pressure
   - is the difference between the systolic and diastolic pressures.
   - The most important determinant of pulse pressure is stroke volume. As blood is ejected from the left ventricle into the arterial system, arterial pressure increases because of the relatively low capacitance of the arteries. Because diastolic pressure remains unchanged during ventricular systole, the pulse pressure increases to the same extent as the systolic pressure.
   - Decreases in capacitance, such as those that occur with the aging process, cause increases in pulse pressure.

![FIGURE 3-2 Arterial pressure during the cardiac cycle.](image-url)
4. **Mean arterial pressure**
   - *is the average arterial pressure with respect to time.*
   - *can be calculated approximately as diastolic pressure plus one-third of pulse pressure.*

H. **Venous pressure**
   - *is very low.*
   - *The veins have a high capacitance and, therefore, can hold large volumes of blood at low pressure.*

I. **Atrial pressure**
   - *is slightly lower than venous pressure.*
   - *Left atrial pressure is estimated by the pulmonary wedge pressure. A catheter, inserted into the smallest branches of the pulmonary artery, makes almost direct contact with the pulmonary capillaries. The measured pulmonary capillary pressure is approximately equal to the left atrial pressure.*

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### III. CARDIAC ELECTROPHYSIOLOGY

A. **Electrocardiogram (ECG) (Figure 3-3)**

1. **P wave**
   - *represents atrial depolarization.*
   - *does not include atrial repolarization, which is “buried” in the QRS complex.*

2. **PR interval**
   - *is the interval from the beginning of the P wave to the beginning of the Q wave (initial depolarization of the ventricle).*

   ![Figure 3-3](image-url)  
   **FIGURE 3-3** Normal electrocardiogram measured from lead II.
varies with **conduction velocity through the atrioventricular (AV) node**. For example, if AV nodal conduction decreases (as in **heart block**), the PR interval increases.

- Stimulation of the sympathetic nervous system decreases **i.e., increased conduction velocity through AV node**.
- Stimulation of the parasympathetic nervous system increases **i.e., decreased conduction velocity through AV node**.

### 3. QRS Complex
- Represents depolarization of the ventricles.

### 4. QT Interval
- Is the interval from the beginning of the Q wave to the end of the T wave.
- Represents the entire period of depolarization and repolarization of the ventricles.

### 5. ST Segment
- Is the segment from the end of the S wave to the beginning of the T wave.
- Is isoelectric.
- Represents the period when the ventricles are depolarized.

### 6. T Wave
- Represents ventricular repolarization.

### B. Cardiac Action Potentials (see Table 1-3)

- The **resting membrane potential** is determined by the conductance to K⁺ and approaches the K⁺ equilibrium potential.
- **Inward current** brings positive charge into the cell and **depolarizes** the membrane potential.
- **Outward current** takes positive charge out of the cell and **hyperpolarizes** the membrane potential.
- The role of Na⁺, K⁺-adenosine triphosphatase (ATPase) is to maintain ionic gradients across cell membranes.

#### 1. Ventricles, Atria, and the Purkinje System (Figure 3-4)
- Have stable resting membrane potentials of about –90 millivolts (mV). This value approaches the K⁺ equilibrium potential.
- Action potentials are of long duration, especially in Purkinje fibers, where they last 300 milliseconds (msec).

##### a. Phase 0
- Is the **upstroke** of the action potential.
is caused by a transient increase in \textit{Na}^{+} conductance. This increase results in an inward \textit{Na}^{+} current that depolarizes the membrane.

At the peak of the action potential, the membrane potential approaches the \textit{Na}^{+} equilibrium potential.

b. Phase 1

is a brief period of initial repolarization.

\textit{Initial repolarization} is caused by an outward current, in part because of the movement of \textit{K}^{+} ions (favored by both chemical and electrical gradients) out of the cell and in part because of a decrease in \textit{Na}^{+} conductance.

c. Phase 2

is the \textit{plateau} of the action potential.

is caused by a \textit{transient increase in Ca}^{2+} conductance, which results in an \textit{inward Ca}^{2+} current, and by an increase in \textit{K}^{+} conductance.

During phase 2, outward and inward currents are approximately equal, so the membrane potential is stable at the plateau level.

d. Phase 3

is \textit{repolarization}.

During phase 3, \textit{Ca}^{2+} conductance decreases, and \textit{K}^{+} conductance increases and therefore predominates.

The high \textit{K}^{+} conductance results in a large \textit{outward K}^{+ current} (\textit{I}_{\text{K}}), which hyperpolarizes the membrane back toward the \textit{K}^{+} equilibrium potential.

e. Phase 4

is the \textit{resting membrane potential}.

is a period during which inward and outward currents (\textit{I}_{\text{K1}}) are equal and the membrane potential approaches the \textit{K}^{+} equilibrium potential.

2. Sinoatrial (SA) node (Figure 3-5)

is normally the \textit{pacemaker} of the heart.

has an \textit{unstable resting potential}.

exhibits phase 4 depolarization, or automaticity.

The AV node and the His-Purkinje systems are \textit{latent pacemakers} that may exhibit automaticity and override the SA node if it is suppressed.

The intrinsic rate of phase 4 depolarization (and heart rate) is fastest in the SA node and slowest in the His-Purkinje system:

SA node > AV node > His-Purkinje

\textbf{FIGURE 3-5} Sinoatrial nodal action potential.
a. Phase 0
- is the **upstroke** of the action potential.
- is caused by an increase in **Ca\(^{2+}\)** conductance. This increase causes an **inward Ca\(^{2+}\) current** that drives the membrane potential toward the Ca\(^{2+}\) equilibrium potential.
- The ionic basis for phase 0 in the SA node is different from that in the ventricles, atria, and Purkinje fibers (where it is the result of an inward Na\(^{+}\) current).

b. Phase 3
- is **repolarization**.
- is caused by an increase in K\(^{+}\) conductance. This increase results in an **outward K\(^{+}\) current** that causes repolarization of the membrane potential.

c. Phase 4
- is **slow depolarization**.
- accounts for the pacemaker activity of the SA node (automaticity).
- is caused by an increase in Na\(^{+}\) conductance, which results in an **inward Na\(^{+}\) current** called \(I_f\).
- \(I_f\) is **turned on by repolarization** of the membrane potential during the preceding action potential.

d. Phases 1 and 2
- are not present in the SA node action potential.

3. AV node
- Upstroke of the action potential in the AV node is the result of an **inward Ca\(^{2+}\) current** (as in the SA node).

C. Conduction velocity
- reflects the time required for excitation to spread throughout cardiac tissue.
- depends on the **size of the inward current during the upstroke** of the action potential. The larger the inward current, the higher the conduction velocity.
- is **fastest in the Purkinje system**.
- is **slowest in the AV node** (seen as the PR interval on the ECG), allowing time for ventricular filling before ventricular contraction. If conduction velocity through the AV node is increased, ventricular filling may be compromised.

D. Excitability
- is the ability of cardiac cells to initiate action potentials in response to inward, depolarizing current.
- reflects the recovery of channels that carry the inward currents for the upstroke of the action potential.
- changes over the course of the action potential. These changes in excitability are described by **refractory periods** (Figure 3-6).

1. Absolute refractory period (ARP)
- begins with the upstroke of the action potential and ends after the plateau.
- reflects the time during which **no action potential can be initiated**, regardless of how much inward current is supplied.

2. Effective refractory period (ERP)
- is slightly longer than the ARP.
- is the period during which a **conducted action potential cannot be elicited**.

3. Relative refractory period (RRP)
- is the period immediately after the ARP when repolarization is almost complete.
is the period during which an action potential can be elicited, but more than the usual inward current is required.

E. Autonomic effects on heart rate and conduction velocity (Table 3-1)

See IV C for a discussion of inotropic effects.

1. Definitions of chronotropic and dromotropic effects
   a. Chronotropic effects
      - produce changes in heart rate.
      - A negative chronotropic effect decreases heart rate by decreasing the firing rate of the SA node.
      - A positive chronotropic effect increases heart rate by increasing the firing rate of the SA node.

   b. Dromotropic effects
      - produce changes in conduction velocity, primarily in the AV node.
      - A negative dromotropic effect decreases conduction velocity through the AV node, slowing the conduction of action potentials from the atria to the ventricles and increasing the PR interval.
      - A positive dromotropic effect increases conduction velocity through the AV node, speeding the conduction of action potentials from the atria to the ventricles and decreasing the PR interval.

2. Parasympathetic effects on heart rate and conduction velocity

   The SA node, atria, and AV node have parasympathetic vagal innervation, but the ventricles do not. The neurotransmitter is acetylcholine (ACh), which acts at muscarinic receptors.

| Table 3-1 Autonomic Effects on the Heart and Blood Vessels |
|---------------------------------|-----------------|-----------------|
| **Efferent Effect**             | **Sympathetic** | **Parasympathetic** |
| Heart rate                      | ↑ β₁            | ↓ Muscarinic     |
| Conduction velocity (AV node)   | ↑ β₁            | ↓ Muscarinic     |
| Contractility                   | ↑ β₂            | ↓ (atria only) Muscarinic |
| Vascular smooth muscle          | Constriction    | α₁             |
| Skin, splanchnic                | Constriction    | α₁             |
| Skeletal muscle                 | Relaxation      | β₂             |

AV = atrioventricular.
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a. **Negative chronotropic effect**
   - decreases heart rate by decreasing the rate of phase 4 depolarization.
   - Fewer action potentials occur per unit time because the threshold potential is reached more slowly and, therefore, less frequently.
   - The mechanism of the negative chronotropic effect is decreased \( I_f \), the inward Na\(^+\) current that is responsible for phase 4 depolarization in the SA node.

b. **Negative dromotropic effect**
   - decreases conduction velocity through the AV node.
   - Action potentials are conducted more slowly from the atria to the ventricles.
   - increases the PR interval.
   - The mechanism of the negative dromotropic effect is decreased inward Ca\(^{2+}\) current and increased outward K\(^+\) current.

3. **Sympathetic effects on heart rate and conduction velocity**
   - **Norepinephrine** is the neurotransmitter, acting at \( \beta_1 \) receptors.
     a. **Positive chronotropic effect**
        - increases heart rate by increasing the rate of phase 4 depolarization.
        - More action potentials occur per unit time because the threshold potential is reached more quickly and, therefore, more frequently.
        - The mechanism of the positive chronotropic effect is increased \( I_f \), the inward Na\(^+\) current that is responsible for phase 4 depolarization in the SA node.
     b. **Positive dromotropic effect**
        - increases conduction velocity through the AV node.
        - Action potentials are conducted more rapidly from the atria to the ventricles, and ventricular filling may be compromised.
        - decreases the PR interval.
        - The mechanism of the positive dromotropic effect is increased inward Ca\(^{2+}\) current.

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**IV. CARDIAC MUSCLE AND CARDIAC OUTPUT**

**A. Myocardial cell structure**

1. **Sarcomere**
   - is the contractile unit of the myocardial cell.
   - is similar to the contractile unit in skeletal muscle.
   - runs from Z line to Z line.
   - contains thick filaments (myosin) and thin filaments (actin, troponin, tropomyosin).
   - As in skeletal muscle, shortening occurs according to a sliding filament model, which states that thin filaments slide along adjacent thick filaments by forming and breaking cross-bridges between actin and myosin.

2. **Intercalated disks**
   - occur at the ends of the cells.
   - maintain cell-to-cell cohesion.

3. **Gap junctions**
   - are present at the intercalated disks.
   - are low-resistance paths between cells that allow for rapid electrical spread of action potentials.
   - account for the observation that the heart behaves as an electrical syncytium.
4. Mitochondria
   ■ are more numerous in cardiac muscle than in skeletal muscle.

5. T tubules
   ■ are continuous with the cell membrane.
   ■ invaginate the cells at the Z lines and carry action potentials into the cell interior.
   ■ are well developed in the ventricles, but poorly developed in the atria.
   ■ form dyads with the sarcoplasmic reticulum.

6. Sarcoplasmic reticulum (SR)
   ■ are small-diameter tubules in close proximity to the contractile elements.
   ■ are the site of storage and release of Ca\(^{2+}\) for excitation–contraction coupling.

B. Steps in excitation–contraction coupling

1. The action potential spreads from the cell membrane into the T tubules.
2. During the plateau of the action potential, Ca\(^{2+}\) conductance is increased and Ca\(^{2+}\) enters the cell from the extracellular fluid (inward Ca\(^{2+}\) current) through L-type Ca\(^{2+}\) channels (dihydropyridine receptors).
3. This Ca\(^{2+}\) entry triggers the release of even more Ca\(^{2+}\) from the SR (Ca\(^{2+}\)-induced Ca\(^{2+}\) release) through Ca\(^{2+}\) release channels (ryanodine receptors).
   ■ The amount of Ca\(^{2+}\) released from the SR depends on the amount of Ca\(^{2+}\) previously stored and on the size of the inward Ca\(^{2+}\) current during the plateau of the action potential.
4. As a result of this Ca\(^{2+}\) release, intracellular [Ca\(^{2+}\)] increases.
5. Ca\(^{2+}\) binds to troponin C, and tropomyosin is moved out of the way, removing the inhibition of actin and myosin binding.
6. Actin and myosin bind, the thick and thin filaments slide past each other, and the myocardial cell contracts. The magnitude of the tension that develops is proportional to the intracellular [Ca\(^{2+}\)].
7. Relaxation occurs when Ca\(^{2+}\) is reaccumulated by the SR by an active Ca\(^{2+}\)-ATPase pump.

C. Contractility
   ■ is the intrinsic ability of cardiac muscle to develop force at a given muscle length.
   ■ is also called inotropism.
   ■ is related to the intracellular Ca\(^{2+}\) concentration.
   ■ can be estimated by the ejection fraction (stroke volume/end-diastolic volume), which is normally 0.55 (55%).
   ■ Positive inotropic agents produce an increase in contractility.
   ■ Negative inotropic agents produce a decrease in contractility.

1. Factors that increase contractility (positive inotropism) [see Table 3-1]
   a. Increased heart rate
      ■ When more action potentials occur per unit time, more Ca\(^{2+}\) enters the myocardial cells during the action potential plateaus, more Ca\(^{2+}\) is released from the SR, and greater tension is produced during contraction.
      ■ Examples of the effect of increased heart rate are:
        (1) Positive staircase, or Bowditch staircase (or Treppe). Increased heart rate increases the force of contraction in a stepwise fashion as the intracellular [Ca\(^{2+}\)] increases cumulatively over several beats.
        (2) Postextrasystolic potentiation. The beat that occurs after an extrasystolic beat has increased force of contraction because “extra” Ca\(^{2+}\) entered the cells during the extrasystole.
b. **Sympathetic stimulation (catecholamines) via β₁ receptors** (see Table 3-1)

- Increases the force of contraction by two mechanisms:
  1. It increases the inward Ca²⁺ current during the plateau of each cardiac action potential.
  2. It increases the activity of the Ca²⁺ pump of the SR (by phosphorylation of phospholamban); as a result, more Ca²⁺ is accumulated by the SR and thus more Ca²⁺ is available for release in subsequent beats.

c. **Cardiac glycosides (digitalis)**

- Increase the force of contraction by inhibiting Na⁺,K⁺-ATPase in the myocardial cell membrane (Figure 3-7).
- As a result of this inhibition, the intracellular [Na⁺] increases, diminishing the Na⁺ gradient across the cell membrane.
- Na⁺–Ca²⁺ exchange (a mechanism that extrudes Ca²⁺ from the cell) depends on the size of the Na⁺ gradient and thus is diminished, producing an increase in intracellular [Ca²⁺].

2. **Factors that decrease contractility (negative inotropism)** [see Table 3-1]

- **Parasympathetic stimulation (ACh) via muscarinic receptors** decreases the force of contraction in the atria by decreasing the inward Ca²⁺ current during the plateau of the cardiac action potential.

D. **Length–tension relationship in the ventricles (Figure 3-8)**

- Describes the effect of ventricular muscle cell length on the force of contraction.
- Is similar to the relationship in skeletal muscle.

1. **Preload**

- Is *end-diastolic volume*, which is related to *right atrial pressure*.
- When venous return increases, end-diastolic volume increases and stretches or lengthens the ventricular muscle fibers (see Frank–Starling relationship, IV D 5).

2. **Afterload**

- For the left ventricle is *aortic pressure*. Increases in aortic pressure cause an increase in afterload on the left ventricle.
- For the right ventricle is *pulmonary artery pressure*. Increases in pulmonary artery pressure cause an increase in afterload on the right ventricle.

3. **Sarcomere length**

- Determines the maximum number of cross-bridges that can form between actin and myosin.
- Determines the maximum tension, or force of contraction.

4. **Velocity of contraction at a fixed muscle length**

- Is maximal when the afterload is zero.
- Is decreased by increases in afterload.
5. Frank–Starling relationship

- describes the increases in stroke volume and cardiac output that occur in response to an increase in venous return or end-diastolic volume (see Figure 3-8).
- is based on the length–tension relationship in the ventricle. Increases in end-diastolic volume cause an increase in ventricular fiber length, which produces an increase in developed tension.
- is the mechanism that matches cardiac output to venous return. The greater the venous return, the greater the cardiac output.
- Changes in contractility shift the Frank–Starling curve upward (increased contractility) or downward (decreased contractility).

_a. Increases in contractility_ cause an increase in cardiac output for any level of right atrial pressure or end-diastolic volume.

_b. Decreases in contractility_ cause a decrease in cardiac output for any level of right atrial pressure or end-diastolic volume.

E. Ventricular pressure–volume loops (Figure 3-9)

- are constructed by combining systolic and diastolic pressure curves.
- The diastolic pressure curve is the relationship between diastolic pressure and diastolic volume in the ventricle.

---

**FIGURE 3-8** Frank–Starling relationship and the effect of positive and negative inotropic agents.

**FIGURE 3-9** Left ventricular pressure–volume loop.
The systolic pressure curve is the corresponding relationship between systolic pressure and systolic volume in the ventricle.

A single left ventricular cycle of contraction, ejection, relaxation, and refilling can be visualized by combining the two curves into a pressure–volume loop.

1. Steps in the cycle
   a. 1 → 2 (isovolumetric contraction). The cycle begins during diastole at point 1. The left ventricle is filled with blood from the left atrium and its volume is about 140 mL (end-diastolic volume). Ventricular pressure is low because the ventricular muscle is relaxed. On excitation, the ventricle contracts and ventricular pressure increases. The mitral valve closes when left ventricular pressure is greater than left atrial pressure. Because all valves are closed, no blood can be ejected from the ventricle (isovolumetric).
   b. 2 → 3 (ventricular ejection). The aortic valve opens at point 2 when pressure in the left ventricle exceeds pressure in the aorta. Blood is ejected into the aorta, and ventricular volume decreases. The volume that is ejected in this phase is the stroke volume. Thus, stroke volume can be measured graphically by the width of the pressure–volume loop. The volume remaining in the left ventricle at point 3 is end-systolic volume.
   c. 3 → 4 (isovolumetric relaxation). At point 3, the ventricle relaxes. When ventricular pressure decreases to less than aortic pressure, the aortic valve closes. Because all of the valves are closed again, ventricular volume is constant (isovolumetric) during this phase.
   d. 4 → 1 (ventricular filling). Once left ventricular pressure decreases to less than left atrial pressure, the mitral (AV) valve opens and filling of the ventricle begins. During this phase, ventricular volume increases to about 140 mL (the end-diastolic volume).

2. Changes in the ventricular pressure–volume loop are caused by several factors (Figure 3-10).
   a. Increased preload (see Figure 3-10A)
   - refers to an increase in end-diastolic volume and is the result of increased venous return.
   - causes an increase in stroke volume based on the Frank–Starling relationship.
   - The increase in stroke volume is reflected in increased width of the pressure–volume loop.
   b. Increased afterload (see Figure 3-10B)
   - refers to an increase in aortic pressure.
   - The ventricle must eject blood against a higher pressure, resulting in a decrease in stroke volume.
   - The decrease in stroke volume is reflected in decreased width of the pressure–volume loop.
   - The decrease in stroke volume results in an increase in end-systolic volume.

![Figure 3-10](image-url) Effects of changes in (A) preload, (B) afterload, and (C) contractility on the ventricular pressure–volume loop.
c. Increased contractility (see Figure 3-10C)
   - The ventricle develops greater tension than usual during systole, causing an **increase in stroke volume**.
   - The increase in stroke volume results in a decrease in end-systolic volume.

F. Cardiac and vascular function curves (Figure 3-11)
   - are simultaneous plots of cardiac output and venous return as a function of right atrial pressure or end-diastolic volume.

1. The cardiac function (cardiac output) curve
   - depicts the Frank–Starling relationship for the ventricle.
   - shows that cardiac output is a function of end-diastolic volume.

2. The vascular function (venous return) curve
   - depicts the relationship between blood flow through the vascular system (or venous return) and right atrial pressure.

a. Mean systemic pressure
   - is the point at which the vascular function curve intersects the x-axis.
   - equals right atrial pressure when there is “no flow” in the cardiovascular system.
   - is measured when the heart is stopped experimentally. Under these conditions, cardiac output and venous return are zero, and pressure is equal throughout the cardiovascular system.

   (1) Mean systemic pressure is increased by an **increase in blood volume** or by a **decrease in venous compliance** (where blood is shifted from the veins to the arteries). An increase in mean systemic pressure is reflected in a **shift of the vascular function** curve to the right (Figure 3-12).

   (2) Mean systemic pressure is decreased by a **decrease in blood volume** or by an **increase in venous compliance** (where blood is shifted from the arteries to the veins). A decrease in mean systemic pressure is reflected in a **shift of the vascular function** curve to the left.

b. Slope of the venous return curve
   - is determined by the **resistance of the arterioles**.
A clockwise rotation of the venous return curve indicates a decrease in total peripheral resistance (TPR). When TPR is decreased for a given right atrial pressure, there is an increase in venous return (i.e., vasodilation of the arterioles "allows" more blood to flow from the arteries to the veins and back to the heart).

A counterclockwise rotation of the venous return curve indicates an increase in TPR (Figure 3-13). When TPR is increased for a given right atrial pressure, there is a decrease in venous return to the heart (i.e., vasoconstriction of the arterioles decreases blood flow from the arteries to the veins and back to the heart).

3. Combining cardiac output and venous return curves
   - When cardiac output and venous return are simultaneously plotted as a function of right atrial pressure, they intersect at a single value of right atrial pressure.
   - The point at which the two curves intersect is the equilibrium, or steady-state point (see Figure 3-11). Equilibrium occurs when cardiac output equals venous return.
Cardiac output can be changed by altering the cardiac output curve, the venous return curve, or both curves simultaneously. The superimposed curves can be used to predict the direction and magnitude of changes in cardiac output.

a. **Inotropic agents change the cardiac output curve.**
   (1) **Positive inotropic agents** (e.g., digitalis) produce increased contractility and increased cardiac output (Figure 3-14).
   - The equilibrium, or intersection, point shifts to a higher cardiac output and a correspondingly lower right atrial pressure.
   - Right atrial pressure decreases because more blood is ejected from the heart on each beat (increased stroke volume).

   (2) **Negative inotropic agents** produce decreased contractility and decreased cardiac output (not illustrated).

b. **Changes in blood volume or venous compliance change the venous return curve.**
   (1) **Increases in blood volume or decreases in venous compliance** increase mean systemic pressure, shifting the venous return curve to the right in a parallel fashion (see Figure 3-12). A new equilibrium, or intersection, point is established at which both cardiac output and right atrial pressure are increased.

   (2) **Decreases in blood volume** (e.g., hemorrhage) or **increases in venous compliance** have the opposite effect—decreased mean systemic pressure and a shift of the venous return curve to the left in a parallel fashion. A new equilibrium point is established at which both cardiac output and right atrial pressure are decreased (not illustrated).

c. **Changes in TPR change both the cardiac output and the venous return curves.**
   - Changes in TPR alter both curves simultaneously; therefore, the responses are more complicated than those noted in the previous examples.

   (1) **Increasing TPR causes a decrease in both cardiac output and venous return** (see Figure 3-13).
      - A **counterclockwise rotation of the venous return curve** occurs. Increased TPR results in decreased venous return as blood is retained on the arterial side.
      - A **downward shift of the cardiac output curve** is caused by the increased aortic pressure (increased afterload) as the heart pumps against a higher pressure.
      - As a result of these simultaneous changes, a new equilibrium point is established at which both cardiac output and venous return are decreased, but right atrial pressure is unchanged.

![FIGURE 3-14 Effect of a positive inotropic agent on the cardiac function curve, cardiac output, and right atrial pressure.](image)
(2) Decreasing TPR causes an increase in both cardiac output and venous return (not illustrated).

(a) A clockwise rotation of the venous return curve occurs. Decreased TPR results in increased venous return as more blood is allowed to flow back to the heart from the arterial side.

(b) An upward shift of the cardiac output curve is caused by the decreased aortic pressure (decreased afterload) as the heart pumps against a lower pressure.

(c) As a result of these simultaneous changes, a new equilibrium point is established at which both cardiac output and venous return are increased, but right atrial pressure is unchanged.

G. Stroke volume, cardiac output, and ejection fraction

1. Stroke volume
   - is the volume ejected from the ventricle on each beat.
   - is expressed by the following equation:
     \[
     \text{Stroke volume} = \text{End-diastolic volume} - \text{End-systolic volume}
     \]

2. Cardiac output
   - is expressed by the following equation:
     \[
     \text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}
     \]

3. Ejection fraction
   - is the fraction of the end-diastolic volume ejected in each stroke volume.
   - is related to contractility.
   - is normally 0.55 or 55%.
   - is expressed by the following equation:
     \[
     \text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}
     \]

H. Stroke work

- is the work the heart performs on each beat.
- is equal to pressure \times volume. For the left ventricle, pressure is aortic pressure and volume is stroke volume.
- is expressed by the following equation:
  \[
  \text{Stroke work} = \text{Aortic pressure} \times \text{Stroke volume}
  \]

- Fatty acids are the primary energy source for stroke work.

I. Cardiac oxygen (O₂) consumption

- is directly related to the amount of tension developed by the ventricles.
- is increased by:
  1. Increased afterload (increased aortic pressure)
  2. Increased size of the heart (Laplace's law states that tension is proportional to the radius of a sphere.)
  3. Increased contractility
  4. Increased heart rate
J. Measurement of cardiac output by the Fick principle

The Fick principle for measuring cardiac output is expressed by the following equation:

\[
\text{Cardiac output} = \frac{\text{\textit{O}_2 \text{ consumption}}}{\text{\textit{O}_2 \text{ pulmonary vein}} - \text{\textit{O}_2 \text{ pulmonary artery}}}
\]

The equation is solved as follows:
1. \(\text{\textit{O}_2 \text{ consumption}}\) for the whole body is measured.
2. Pulmonary vein \(\text{\textit{O}_2}\) is measured in a peripheral artery.
3. Pulmonary artery \(\text{\textit{O}_2}\) is measured in systemic mixed venous blood.

For example, a 70-kg man has a resting \(\text{\textit{O}_2}\) consumption of 250 mL/min, a peripheral arterial \(\text{\textit{O}_2}\) content of 0.20 mL \(\text{\textit{O}_2}\)/mL of blood, a mixed venous \(\text{\textit{O}_2}\) content of 0.15 mL \(\text{\textit{O}_2}\)/mL of blood, and a heart rate of 72 beats/min. What is his cardiac output? What is his stroke volume?

\[
\text{Cardiac output} = \frac{250 \text{ mL/min}}{0.20 \text{ mL } \text{\textit{O}_2}/\text{mL} - 0.15 \text{ mL } \text{\textit{O}_2}/\text{mL}} = 5000 \text{ mL/min}, \text{ or 5.0 L/min}
\]

\[
\text{Stroke volume} = \frac{\text{Cardiac output}}{\text{Heart rate}} = \frac{5000 \text{ mL/min}}{72 \text{ beats/min}} = 69.4 \text{ mL/beat}
\]

V. CARDIAC CYCLE

Figure 3-15 shows the mechanical and electrical events of a single cardiac cycle. The seven phases are separated by vertical lines.

- Use the ECG as an event marker.
- Opening and closing of valves causes the physiologic heart sounds.
- When all valves are closed, ventricular volume is constant, and the phase is called isovolumetric.

A. Atrial systole
- is preceded by the P wave, which represents electrical activation of the atria.
- contributes to, but is not essential for, ventricular filling.
- The increase in atrial pressure (venous pressure) caused by atrial systole is the a wave on the venous pulse curve.
- Filling of the ventricle by atrial systole causes the fourth heart sound, which is not audible in normal adults.

B. Isovolumetric ventricular contraction
- begins after the onset of the QRS wave, which represents electrical activation of the ventricles.
- When ventricular pressure becomes greater than atrial pressure, the AV valves close. Their closure corresponds to the first heart sound. Because the mitral valve closes before the tricuspid valve, the first heart sound may be split.
FIGURE 3-15 The cardiac cycle. ECG = electrocardiogram; A = atrial systole; B = isovolumetric ventricular contraction; C = rapid ventricular ejection; D = reduced ventricular ejection; E = isovolumetric ventricular relaxation; F = rapid ventricular filling; G = reduced ventricular filling.
Ventricular pressure increases isovolumetrically as a result of ventricular contraction. However, no blood leaves the ventricle during this phase because the aortic valve is closed.

C. Rapid ventricular ejection
- Ventricular pressure reaches its maximum value during this phase.
- When ventricular pressure becomes greater than aortic pressure, the aortic valve opens.
- Rapid ejection of blood into the aorta occurs because of the pressure gradient between the ventricle and the aorta.
- Ventricular volume decreases dramatically because most of the stroke volume is ejected during this phase.
- Atrial filling begins.
- The onset of the T wave, which represents repolarization of the ventricles, marks the end of both ventricular contraction and rapid ventricular ejection.

D. Reduced ventricular ejection
- Ejection of blood from the ventricle continues, but is slower.
- Ventricular pressure begins to decrease.
- Aortic pressure also decreases because of the runoff of blood from large arteries into smaller arteries.
- Atrial filling continues.

E. Isovolumetric ventricular relaxation
- Repolarization of the ventricles is now complete (end of the T wave).
- The aortic valve closes, followed by closure of the pulmonic valve. Closure of the semilunar valves corresponds to the second heart sound. Inspiration causes splitting of the second heart sound.
- The AV valves remain closed during most of this phase.
- Ventricular pressure decreases rapidly because the ventricle is now relaxed.
- Ventricular volume is constant (isovolumetric) because all of the valves are closed.
- The “blip” in the aortic pressure tracing occurs after closure of the aortic valve and is called the dicrotic notch, or incisura.
- When ventricular pressure becomes less than atrial pressure, the mitral valve opens.

F. Rapid ventricular filling
- The mitral valve is open and ventricular filling from the atrium begins.
- Aortic pressure continues to decrease because blood continues to run off into the smaller arteries.
- Rapid flow of blood from the atria into the ventricles causes the third heart sound, which is normal in children but, in adults, is associated with disease.

G. Reduced ventricular filling (diastasis)
- is the longest phase of the cardiac cycle.
- Ventricular filling continues, but at a slower rate.
- The time required for diastasis and ventricular filling depends on heart rate. Increases in heart rate decrease the time available for ventricular refilling.

VI. REGULATION OF ARTERIAL PRESSURE

- The most important mechanisms for regulating arterial pressure are a fast, neurally mediated baroreceptor mechanism and a slower, hormonally regulated renin–angiotensin–aldosterone mechanism.
A. Baroreceptor reflex

- includes fast, neural mechanisms.
- is a negative feedback system that is responsible for the minute-to-minute regulation of arterial blood pressure.
- Baroreceptors are stretch receptors located within the walls of the carotid sinus near the bifurcation of the common carotid arteries.

1. Steps in the baroreceptor reflex (Figure 3-16)
   a. A decrease in arterial pressure decreases stretch on the walls of the carotid sinus.
      - Because the baroreceptors are most sensitive to changes in arterial pressure, rapidly decreasing arterial pressure produces the greatest response.
      - Additional baroreceptors in the aortic arch respond to increases, but not to decreases, in arterial pressure.
   b. Decreased stretch decreases the firing rate of the carotid sinus nerve (Hering's nerve, cranial nerve [CN] IX), which carries information to the vasomotor center in the brain stem.
   c. The set point for mean arterial pressure in the vasomotor center is about 100 mm Hg. Therefore, if mean arterial pressure is less than 100 mm Hg, a series of autonomic

![Figure 3-16](Role of the baroreceptor reflex in the cardiovascular response to hemorrhage. $P_a =$ mean arterial pressure; TPR = total peripheral resistance.)
responses is coordinated by the vasomotor center. These changes will attempt to increase blood pressure toward normal.

d. The responses of the vasomotor center to a decrease in mean arterial blood pressure are coordinated to increase the arterial pressure to 100 mm Hg. The responses are decreased parasympathetic (vagal) outflow to the heart and increased sympathetic outflow to the heart and blood vessels.

The following four effects attempt to increase the arterial pressure to normal:

1. ↑ heart rate, resulting from decreased parasympathetic tone and increased sympathetic tone to the SA node of the heart.
2. ↑ contractility and stroke volume, resulting from increased sympathetic tone to the heart. Together with the increase in heart rate, the increases in contractility and stroke volume produce an increase in cardiac output that increases arterial pressure.
3. ↑ vasoconstriction of arterioles, resulting from the increased sympathetic outflow. As a result, TPR and arterial pressure will increase.
4. ↑ vasoconstriction of veins (venoconstriction), resulting from the increased sympathetic outflow. Constriction of the veins causes a decrease in unstressed volume and an increase in venous return to the heart. The increase in venous return causes an increase in cardiac output by the Frank–Starling mechanism.

2. Example of the baroreceptor reflex: response to acute blood loss (see Figure 3-16)

3. Example of the baroreceptor mechanism: Valsalva maneuver

The integrity of the baroreceptor mechanism can be tested with the Valsalva maneuver (i.e., expiring against a closed glottis).

Expiring against a closed glottis causes an increase in intrathoracic pressure, which decreases venous return.

The decrease in venous return causes a decrease in cardiac output and arterial pressure (P_a).

If the baroreceptor reflex is intact, the decrease in P_a is sensed by the baroreceptors, leading to an increase in sympathetic outflow to the heart and blood vessels. In the test, an increase in heart rate would be noted.

When the person stops the maneuver, there is a rebound increase in venous return, cardiac output, and P_a. The increase in P_a is sensed by the baroreceptors, which direct a decrease in heart rate.

B. Renin–angiotensin–aldosterone system

is a slow, hormonal mechanism.

is used in long-term blood pressure regulation by adjustment of blood volume.

Renin is an enzyme.

Angiotensin I is inactive.

Angiotensin II is physiologically active.

Angiotensin II is degraded by angiotensinase. One of the peptide fragments, angiotensin III, has some of the biologic activity of angiotensin II.

1. Steps in the renin–angiotensin–aldosterone system (Figure 3-17)

a. A decrease in renal perfusion pressure causes the juxtaglomerular cells of the afferent arteriole to secrete renin.

b. Renin is an enzyme that catalyzes the conversion of angiotensinogen to angiotensin I in plasma.

c. Angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II, primarily in the lungs.

ACE inhibitors (e.g., captopril) block the conversion of angiotensin I to angiotensin II and, therefore, decrease blood pressure.

Angiotensin receptor (AT_1) antagonists (e.g., losartan) block the action of angiotensin II at its receptor and decrease blood pressure.
d. **Angiotensin II** has four effects:

1. It stimulates the synthesis and secretion of aldosterone by the adrenal cortex.
   - Aldosterone increases Na⁺ reabsorption by the renal distal tubule, thereby increasing extracellular fluid (ECF) volume, blood volume, and arterial pressure.
   - This action of aldosterone is slow because it requires new protein synthesis.

2. It increases Na⁺–H⁺ exchange in the proximal convoluted tubule.
   - This action of angiotensin II directly increases Na⁺ reabsorption, complementing the indirect stimulation of Na⁺ reabsorption via aldosterone.
   - This action of angiotensin II leads to contraction alkalosis.

3. It increases thirst.

4. It causes vasoconstriction of the arterioles, thereby increasing TPR and arterial pressure.

2. **Example: response of the renin–angiotensin–aldosterone system to acute blood loss** (see Figure 3-17)
C. Other regulation of arterial blood pressure

1. Cerebral ischemia
   a. When the brain is ischemic, the partial pressure of carbon dioxide (PCO2) in brain tissue increases.
   b. Chemoreceptors in the vasomotor center respond by **increasing sympathetic outflow** to the heart and blood vessels.
      - Constriction of arterioles causes intense **peripheral vasoconstriction** and increased TPR. Blood flow to other organs (e.g., kidneys) is significantly reduced in an attempt to preserve blood flow to the brain.
      - **Mean arterial pressure can increase to life-threatening levels.**
   c. The **Cushing reaction** is an example of the response to cerebral ischemia. Increases in intracranial pressure cause compression of the cerebral blood vessels, leading to cerebral ischemia and increased cerebral PCO2. The vasomotor center directs an increase in sympathetic outflow to the heart and blood vessels, which causes a profound increase in arterial pressure.

2. Chemoreceptors in the carotid and aortic bodies
   - are located near the bifurcation of the common carotid arteries and along the aortic arch.
   - have very high rates of O2 consumption and are very sensitive to decreases in the partial pressure of oxygen (PO2).
   - Decreases in PO2 activate vasomotor centers that produce vasoconstriction, an increase in TPR, and an increase in arterial pressure.

3. Vasopressin (antidiuretic hormone [ADH])
   - is involved in the regulation of blood pressure in response to hemorrhage, but not in minute-to-minute regulation of normal blood pressure.
   - Atrial receptors respond to a decrease in blood volume (or blood pressure) and cause the release of vasopressin from the posterior pituitary.
   - Vasopressin has two effects that tend to increase blood pressure toward normal:
      a. It is a potent **vasoconstrictor** that increases TPR by activating V1 receptors on the arterioles.
      b. It increases **water reabsorption** by the renal distal tubule and collecting ducts by activating V2 receptors.

4. Atrial natriuretic peptide (ANP)
   - is released from the atria in response to an increase in blood volume and atrial pressure.
   - causes **relaxation of vascular smooth muscle**, dilation of the arterioles, and decreased TPR.
   - causes increased **excretion of Na+ and water** by the kidney, which reduces blood volume and attempts to bring arterial pressure down to normal.
   - inhibits renin secretion.

VII. MICROCIRCULATION AND LYMPH

A. Structure of capillary beds
   - Metarterioles branch into the capillary beds. At the junction of the arterioles and capillaries is a smooth muscle band called the **precapillary sphincter**.
   - True capillaries do not have smooth muscle; they consist of a single layer of **endothelial cells** surrounded by a basement membrane.
   - Clefts (pores) between the endothelial cells allow passage of water-soluble substances. The clefts represent a very small fraction of the surface area (<0.1%).
Blood flow through the capillaries is regulated by contraction and relaxation of the arterioles and the precapillary sphincters.

B. Passage of substances across the capillary wall

1. Lipid-soluble substances
   - cross the membranes of the capillary endothelial cells by simple diffusion.
   - include O₂ and CO₂.

2. Small water-soluble substances
   - cross via the water-filled clefts between the endothelial cells.
   - include water, glucose, and amino acids.
   - Generally, protein molecules are too large to pass freely through the clefts.
   - In the brain, the clefts between endothelial cells are exceptionally tight (blood-brain barrier).
   - In the liver and intestine, the clefts are exceptionally wide and allow passage of protein. These capillaries are called sinusoids.

3. Large water-soluble substances
   - can cross by pinocytosis.

C. Fluid exchange across capillaries

1. The Starling equation (Figure 3-18)

   \[ J_v = K_f [(P_c - P_i) - (\pi_c - \pi_i)] \]

   where:
   \( J_v \) = fluid movement (mL/min)
   \( K_f \) = hydraulic conductance (mL/min • mm Hg)
   \( P_c \) = capillary hydrostatic pressure (mm Hg)
   \( P_i \) = interstitial hydrostatic pressure (mm Hg)
   \( \pi_c \) = capillary oncotic pressure (mm Hg)
   \( \pi_i \) = interstitial oncotic pressure (mm Hg)

   a. \( J_v \) is fluid flow.
      - When \( J_v \) is positive, there is net fluid movement out of the capillary (filtration).
      - When \( J_v \) is negative, there is net fluid movement into the capillary (absorption).

   b. \( K_f \) is the filtration coefficient.
      - It is the hydraulic conductance (water permeability) of the capillary wall.

   c. \( P_c \) is capillary hydrostatic pressure.
      - An increase in \( P_c \) favors filtration out of the capillary.
      - \( P_c \) is determined by arterial and venous pressures and resistances.
      - An increase in either arterial or venous pressure produces an increase in \( P_c \); increases in venous pressure have a greater effect on \( P_c \).
Pc is higher at the arteriolar end of the capillary than at the venous end (except in glomerular capillaries, where it is nearly constant).

d. **Pi is interstitial fluid hydrostatic pressure.**
   - An increase in Pi opposes filtration out of the capillary.
   - It is normally close to 0 mm Hg (or it is slightly negative).

e. **Pc is capillary oncotic, or colloidosmotic, pressure.**
   - An increase in Pc opposes filtration out of the capillary.
   - Pc is increased by increases in the protein concentration in the blood (e.g., dehydration).
   - Pc is decreased by decreases in the protein concentration in the blood (e.g., nephrotic syndrome, protein malnutrition, liver failure).
   - Small solutes do not contribute to Pc.

f. **Pi is interstitial fluid oncotic pressure.**
   - An increase in Pi favors filtration out of the capillary.
   - Pi is dependent on the protein concentration of the interstitial fluid, which is normally quite low because very little protein is filtered.

2. Factors that increase filtration
   a. ↑Pc—caused by increased arterial or venous pressure
   b. ↓Pi
   c. ↓Pc—caused by decreased protein concentration in the blood
   d. ↑Pi—caused by inadequate lymphatic function

3. Sample calculations using the Starling equation
   a. **Example 1:** At the arteriolar end of a capillary, Pc is 30 mm Hg, Pc is 28 mm Hg, Pi is 0 mm Hg, and Pi is 4 mm Hg. Will filtration or absorption occur?

   \[
   \text{Net pressure} = (30 - 0) - (28 - 4) = +6 \text{ mm Hg}
   \]

   Because the net pressure is positive, **filtration will occur.**

   b. **Example 2:** At the venous end of the same capillary, Pc has decreased to 16 mm Hg, Pc remains at 28 mm Hg, Pi is 0 mm Hg, and Pi is 4 mm Hg. Will filtration or absorption occur?

   \[
   \text{Net pressure} = (16 - 0) - (28 - 4) = -8 \text{ mm Hg}
   \]

   Because the net pressure is negative, **absorption will occur.**

4. **Lymph**
   a. **Function of lymph**
      - Normally, filtration of fluid out of the capillaries is slightly greater than absorption of fluid into the capillaries. The excess filtered fluid is returned to the circulation via the lymph.
      - Lymph also returns any filtered protein to the circulation.

   b. **Unidirectional flow of lymph**
      - **One-way flap valves** permit interstitial fluid to enter, but not leave, the lymph vessels.
      - Flow through larger lymphatic vessels is also unidirectional, and is aided by one-way valves and skeletal muscle contraction.

   c. **Edema** (Table 3-2)
      - Occurs when the volume of interstitial fluid exceeds the capacity of the lymphatics to return it to the circulation.
      - Can be caused by excess filtration or blocked lymphatics.
D. Endothelium-derived relaxing factor (EDRF)

- is produced in the endothelial cells.
- causes local relaxation of vascular smooth muscle.
- Mechanism of action involves the activation of guanylate cyclase and production of cyclic guanosine monophosphate (cGMP).
- One form of EDRF is nitric oxide (NO).
- Circulating ACh causes vasodilation by stimulating the production of NO in vascular smooth muscle.

VIII. SPECIAL CIRCULATIONS (TABLE 3-3)

- Blood flow varies from one organ to another.
- Blood flow to an organ is regulated by altering arteriolar resistance, and can be varied, depending on the organ’s metabolic demands.
- Pulmonary and renal blood flow are discussed in Chapters 4 and 5, respectively.

<table>
<thead>
<tr>
<th>Circulation* (% of Resting Cardiac Output)</th>
<th>Local Metabolic Control</th>
<th>Vasoactive Metabolites</th>
<th>Sympathetic Control</th>
<th>Mechanical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary (5%)</td>
<td>Most important mechanism</td>
<td>Hypoxia</td>
<td>Least important mechanism</td>
<td>Mechanical compression during systole</td>
</tr>
<tr>
<td>Cerebral (15%)</td>
<td>Most important mechanism</td>
<td>CO₂, H⁺</td>
<td>Least important mechanism</td>
<td>Increases in intracranial pressure decrease cerebral blood flow</td>
</tr>
<tr>
<td>Muscle (20%)</td>
<td>Most important mechanism during exercise</td>
<td>Lactate, K⁺, Adenosine</td>
<td>Most important mechanism at rest (α₁ receptor causes vasoconstriction; β₂ receptor causes vasodilation)</td>
<td>Muscular activity causes temporary decrease in blood flow</td>
</tr>
<tr>
<td>Skin (5%)</td>
<td>Least important mechanism</td>
<td></td>
<td>Most important mechanism (temperature regulation)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary† (100%)</td>
<td>Most important mechanism</td>
<td>Hypoxia vasoconstricts</td>
<td>Least important mechanism</td>
<td>Lung inflation</td>
</tr>
</tbody>
</table>

*Renal blood flow (25% of resting cardiac output) is discussed in Chapter 5.
†Pulmonary blood flow is discussed in Chapter 4.
A. Local (intrinsic) control of blood flow

1. Examples of local control
   a. Autoregulation
      - Blood flow to an organ remains constant over a wide range of perfusion pressures.
      - Organs that exhibit autoregulation are the heart, brain, and kidney.
      - For example, if perfusion pressure to the heart is suddenly decreased, compensatory vasodilation of the arterioles will occur to maintain a constant flow.

   b. Active hyperemia
      - Blood flow to an organ is proportional to its metabolic activity.
      - For example, if metabolic activity in skeletal muscle increases as a result of strenuous exercise, blood flow to the muscle will increase proportionately to meet metabolic demands.

   c. Reactive hyperemia
      - is an increase in blood flow to an organ that occurs after a period of occlusion of flow.
      - The longer the period of occlusion is, the greater the increase in blood flow is above preocclusion levels.

2. Mechanisms that explain local control of blood flow
   a. Myogenic hypothesis
      - explains autoregulation, but not active or reactive hyperemia.
      - is based on the observation that vascular smooth muscle contracts when it is stretched.
      - For example, if perfusion pressure to an organ suddenly increases, the arteriolar smooth muscle will be stretched and will contract. The resulting vasoconstriction will maintain a constant flow. (Without vasoconstriction, blood flow would increase as a result of the increased pressure.)

   b. Metabolic hypothesis
      - is based on the observation that the tissue supply of $O_2$ is matched to the tissue demand for $O_2$.
      - Vasodilator metabolites are produced as a result of metabolic activity in tissue. These vasodilators are $CO_2$, $H^+$, $K^+$, lactate, and adenosine.
      - Examples of active hyperemia:
        1. If the metabolic activity of a tissue increases (e.g., strenuous exercise), both the demand for $O_2$ and the production of vasodilator metabolites increase. These metabolites cause arteriolar vasodilation, increased blood flow, and increased $O_2$ delivery to the tissue to meet demand.
        2. If blood flow to an organ suddenly increases as a result of a spontaneous increase in arterial pressure, then more $O_2$ is provided for metabolic activity. At the same time, the increased flow “washes out” vasodilator metabolites. As a result of this “washout,” arteriolar vasoconstriction occurs, resistance increases, and blood flow is decreased to normal.

B. Hormonal (extrinsic) control of blood flow

1. Sympathetic innervation of vascular smooth muscle
   - Increases in sympathetic tone cause vasoconstriction.
   - Decreases in sympathetic tone cause vasodilation.
   - The density of sympathetic innervation varies widely among tissues. Skin has the greatest innervation, whereas coronary, pulmonary, and cerebral vessels have little innervation.
2. Other vasoactive hormones
   a. Histamine
      ■ causes arteriolar dilation and venous constriction. The combined effects of arteriolar
dilation and venous constriction cause increased $P_c$ and increased filtration out of the
capillaries, resulting in local edema.
      ■ is released in response to tissue trauma.
   b. Bradykinin
      ■ causes arteriolar dilation and venous constriction.
      ■ produces increased filtration out of the capillaries (similar to histamine), and caus-
es local edema.
   c. Serotonin (5-hydroxytryptamine)
      ■ causes arteriolar constriction and is released in response to blood vessel damage to
help prevent blood loss.
      ■ has been implicated in the vascular spasms of migraine headaches.
   d. Prostaglandins
      ■ Prostacyclin is a vasodilator in several vascular beds.
      ■ E-series prostaglandins are vasodilators.
      ■ F-series prostaglandins are vasoconstrictors.
      ■ Thromboxane $A_2$ is a vasoconstrictor.

C. Coronary circulation
   ■ is controlled almost entirely by local metabolic factors.
   ■ exhibits autoregulation.
   ■ exhibits active and reactive hyperemia.
   ■ The most important local metabolic factors are hypoxia and adenosine.
   ■ For example, increases in myocardial contractility are accompanied by an increased demand
for $O_2$. To meet this demand, compensatory vasodilation of coronary vessels occurs and,
accordingly, both blood flow and $O_2$ delivery to the contracting heart muscle increase
(active hyperemia).
   ■ During systole, mechanical compression of the coronary vessels reduces blood flow. After
the period of occlusion, blood flow increases to repay the $O_2$ debt (reactive hyperemia).
   ■ Sympathetic nerves play a minor role.

D. Cerebral circulation
   ■ is controlled almost entirely by local metabolic factors.
   ■ exhibits autoregulation.
   ■ exhibits active and reactive hyperemia.
   ■ The most important local vasodilator for the cerebral circulation is $CO_2$. Increases in $PCO_2$
cause vasodilation of the cerebral arterioles and increased blood flow to the brain.
   ■ Sympathetic nerves play a minor role.
   ■ Vasoactive substances in the systemic circulation have little or no effect on cerebral circu-
lation because such substances are excluded by the blood–brain barrier.

E. Skeletal muscle
   ■ is controlled by the extrinsic sympathetic innervation of blood vessels in skeletal muscle and
by local metabolic factors.
   1. Sympathetic innervation
      ■ is the primary regulator of blood flow to the skeletal muscle at rest.
      ■ The arterioles of skeletal muscle are densely innervated by sympathetic fibers. The
veins also are innervated, but less densely.
There are both $\alpha_1$ and $\beta_2$ receptors on the blood vessels of skeletal muscle.

- Stimulation of $\alpha_1$ receptors causes vasoconstriction.
- Stimulation of $\beta_2$ receptors causes vasodilation.
- The state of constriction of skeletal muscle arterioles is a major contributor to the TPR (because of the large mass of skeletal muscle).

2. Local metabolic control

- Blood flow in skeletal muscle exhibits autoregulation and active and reactive hyperemia.
- Demand for $O_2$ in skeletal muscle varies with metabolic activity level, and blood flow is regulated to meet demand.
- During exercise, when demand is high, these local metabolic mechanisms are dominant.
- The local vasodilator substances are lactate, adenosine, and $K^+$.
- Mechanical effects during exercise temporarily compress the arteries and decrease blood flow. During the postocclusion period, reactive hyperemia increases blood flow to repay the $O_2$ debt.

F. Skin

- has extensive sympathetic innervation. Cutaneous blood flow is under extrinsic control.
- Temperature regulation is the principal function of the cutaneous sympathetic nerves. Increased ambient temperature leads to cutaneous vasodilation, allowing dissipation of excess body heat.
- Trauma produces the “triple response” in skin—a red line, a red flare, and a wheal. A wheal is local edema that results from the local release of histamine, which increases capillary filtration.

IX. INTEGRATIVE FUNCTIONS OF THE CARDIOVASCULAR SYSTEM: GRAVITY, EXERCISE, AND HEMORRHAGE

- The responses to changes in gravitational force, exercise, and hemorrhage demonstrate the integrative functions of the cardiovascular system.

A. Changes in gravitational forces (Table 3-4 and Figure 3-19)

- The following changes occur when an individual moves from a supine position to a standing position:

  1. When a person stands, a significant volume of blood pools in the lower extremities because of the high compliance of the veins. (Muscular activity would prevent this pooling.)
  2. As a result of venous pooling and increased local venous pressure, $P_c$ in the legs increases and fluid is filtered into the interstitium. If net filtration of fluid exceeds the ability of the lymphatics to return it to the circulation, edema will occur.
  3. Venous return decreases. As a result of the decrease in venous return, both stroke volume and cardiac output decrease (Frank–Starling relationship, IV D 5).
  4. Arterial pressure decreases because of the reduction in cardiac output. If cerebral blood pressure becomes low enough, fainting may occur.

<table>
<thead>
<tr>
<th>Table 3-4</th>
<th>Summary of Responses to Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Initial Response to Standing</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td>↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↓</td>
</tr>
<tr>
<td>TPR</td>
<td>—</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>↓</td>
</tr>
</tbody>
</table>

TPR = total peripheral resistance.
5. **Compensatory mechanisms** will attempt to increase blood pressure to normal (see Figure 3-19). The **carotid sinus baroreceptors** respond to the decrease in arterial pressure by decreasing the firing rate of the carotid sinus nerves. A coordinated response from the vasomotor center then increases sympathetic outflow to the heart and blood vessels and decreases parasympathetic outflow to the heart. As a result, heart rate, contractility, TPR, and venous return increase, and blood pressure increases toward normal.

6. **Orthostatic hypotension** (fainting or lightheadedness on standing) may occur in individuals whose baroreceptor reflex mechanism is impaired (e.g., individuals treated with sympatholytic agents).

**B. Exercise (Table 3-5 and Figure 3-20)**

1. **The central command (anticipation of exercise)**
   - originates in the motor cortex or from reflexes initiated in muscle proprioceptors when exercise is anticipated.
   - initiates the following changes:
     a. **Sympathetic outflow to the heart and blood vessels is increased.** At the same time, parasympathetic outflow to the heart is decreased. As a result, heart rate and contractility (stroke volume) are increased, and unstressed volume is decreased.
     b. **Cardiac output is increased,** primarily as a result of the increased heart rate and, to a lesser extent, the increased stroke volume.
     c. **Venous return is increased** as a result of muscular activity and venoconstriction. Increased venous return provides more blood for each stroke volume (Frank-Starling relationship, IV D 5).
d. Arteriolar resistance in the skin, splanchnic regions, kidneys, and inactive muscles is increased. Accordingly, blood flow to these organs is decreased.

2. Increased metabolic activity of skeletal muscle
   - Vasodilator metabolites (lactate, K⁺, and adenosine) accumulate because of increased metabolism of the exercising muscle.
   - These metabolites cause arteriolar dilation in the active skeletal muscle, thus increasing skeletal muscle blood flow (active hyperemia).
   - As a result of the increased blood flow, O₂ delivery to the muscle is increased. The number of perfused capillaries is increased so that the diffusion distance for O₂ is decreased.
   - This vasodilation accounts for the overall decrease in TPR that occurs with exercise. Note that activation of the sympathetic nervous system alone (by the central command) would cause an increase in TPR.

![Figure 3-20 Cardiovascular responses to exercise. TPR = total peripheral resistance.](image-url)
C. Hemorrhage (Table 3-6 and Figure 3-21)

The compensatory responses to acute blood loss are as follows:

1. A decrease in blood volume produces a decrease in mean systemic pressure. As a result, there is a decrease in both cardiac output and arterial pressure.
2. The carotid sinus baroreceptors detect the decrease in arterial pressure. As a result of the baroreceptor reflex, there is increased sympathetic outflow to the heart and blood vessels and decreased parasympathetic outflow to the heart, producing:
   a. ↑ heart rate
   b. ↑ contractility
c. ↑TPR (due to arteriolar constriction)

d. Venoconstriction, which increases venous return

e. Constriction of arterioles in skeletal, splanchnic, and cutaneous vascular beds. However, it does not occur in coronary or cerebral vascular beds, ensuring that adequate blood flow will be maintained to the heart and brain.

f. These responses attempt to restore normal arterial blood pressure.

3. Chemoreceptors in the carotid and aortic bodies are very sensitive to hypoxia. They supplement the baroreceptor mechanism by increasing sympathetic outflow to the heart and blood vessels.

4. Cerebral ischemia (if present) causes an increase in $P_{CO_2}$, which activates chemoreceptors in the vasomotor center to increase sympathetic outflow.

5. Arteriolar vasoconstriction causes a decrease in $P_c$. As a result, capillary absorption is favored, which helps to restore circulating blood volume.

6. The adrenal medulla releases epinephrine and norepinephrine, which supplement the actions of the sympathetic nervous system on the heart and blood vessels.

7. The renin–angiotensin–aldosterone system is activated by the decrease in renal perfusion pressure. Because angiotensin II is a potent vasoconstrictor, it reinforces the stimulatory effect of the sympathetic nervous system on TPR. Aldosterone increases NaCl reabsorption in the kidney, increasing the circulating blood volume.

8. ADH is released when atrial receptors detect the decrease in blood volume. ADH causes both vasoconstriction and increased water reabsorption, both of which tend to increase blood pressure.