Located in the Tawara branches. Pacemaker cells have the atrial (SA) and atrioventricular (AV) nodes, and Purkinje cells the right and left atria, pacemaker cells located in the sino-ventricular cardiac myocyte: atrial cardiomyocytes located in the heart contains three modifications of this prototypical each other and send processes deep into the neighboring cell. Of the sarcolemma where individual cells make contact with the T tubules, the SR generates cyclic changes in the cellular and the extracellular space. The sarcolemma forms a series of tubular invaginations, the T tubules or transverse tubules that increase the surface area of the cell and bring the extracellular environment into close proximity to intracellular structures. The sarcoplasmic reticulum (SR) is a network of tubes and cysts spreading throughout the cell. Together with the T tubules, the SR generates cyclic changes in the cellular calcium concentration.

Cardiac myocytes form a functional syncytium in which cells act in concert, both mechanically and electrically. This aspect requires sophisticated communication between cardiac myocytes at the intercalated discs, a specialized portion of the sarcolemma where individual cells make contact with each other and send processes deep into the neighboring cell. The heart contains three modifications of this prototypical ventricular cardiac myocyte: atrial cardiomyocytes located in the right and left atria, pacemaker cells located in the sino-atrial (SA) and atrioventricular (AV) nodes, and Purkinje cells located in the Tawara branches. Pacemaker cells have the ability to generate an action potential (AP), and Purkinje cells have the ability to transmit this AP with high speed. Both pacemaker and Purkinje cells are, in principle, myocytes, but with specialized electrical properties. On the other hand, atrial and ventricular myocytes have specialized mechanical properties, but they also have the ability to generate and propagate APs.

**Electrical Cycle**

The electrical cycle of the heart derives from the excitable nature of each cardiac myocyte. These are typical cells that are specialized in two major ways: to transmit electrical signals and to transduce that electrical signal into a mechanical function, contraction (Fig. 15.2).

**Resting Membrane Potential**

The resting membrane potential ($E_m$) is defined as the voltage difference across the cellular membrane—that is, between the inside and the outside of the cell. The cardiac myocyte is engulfed by the sarcolemma, a lipid bilayer with many voltage- and ligand-gated ion channels. The most significant elements of the sarcolemma that maintain the resting membrane potential and allow for electrical signals to be both generated and transmitted are the voltage-gated ion channels, the Na$^+$–Ca$^{2+}$ exchanger and the Na$^+$-K$^+$-ATPase electrogenic pump. The resting membrane potential results from the open K$^+$ channels in the sarcolemma and the small “leak” of Na$^+$ through ion channels in the sarcolemma. The resting membrane potential is described by the Nernst equation, which takes into account the permeability of the sarcolemma and its ion gradients. The resting membrane potential is calculated to be approximately –85 mV for cardiac myocytes.

**Action Potential**

Within the SA node are pacemaker cells that have the important characteristics of spontaneous diastolic depolarization. The pacemaker cells undergo a gradual depolarization from their “resting” membrane potential of ~65 mV to approximately –40 mV, which is the threshold at which an AP is initiated.

The pacemaking AP is a regenerative, all-or-none, event occurring when the membrane potential depolarizes to a level where a sufficient number of ion channels open, leading to an inward current that can begin a positive feedback loop (2). The predominant ion channels responsible for the AP in the SA node pacemaker cells are T- and L-type Ca$^{2+}$ channels. The dependence on Ca$^{2+}$ for the depolarizing current makes the SA and AV nodes particularly sensitive to pharmacologic manipulation with Ca$^{2+}$ channel blockers. The configuration of the SA node AP is markedly different from that in the atrial and ventricular cardiac myocytes, where voltage-gated...
Na\(^+\) channels predominate and provide the major fast inward current responsible for depolarization. Figure 15.3 provides examples of the APs from the SA node through the atria and the AV node down the bundle of His and Purkinje fibers into the ventricle. The rate of depolarization in the SA and AV nodes is considerably slower than in the rest of the heart. The reversal of the depolarization of the SA nodal pacemaker cells occurs at the peak of depolarization, with opening of delayed rectifier K\(^+\) channels that provide the outward positive current to nullify the previous influx of positive ions, leading to repolarization of the cell. One of the most important ionic currents contributing to the automatic pacemaker ability of the SA node is the so-called “funny current,” or I\(_f\) channel. The I\(_f\) channel is a mixed Na\(^+\)-K\(^+\) inward current activated during diastolic depolarization, at approximately \(-40\) mV, that is hyperpolarization activated and cyclical. It is named “funny current” due to its unusual properties of depolarization (3).

The AP in ventricular cardiac myocytes has a markedly different time course. As an AP passes from the conduction system to the ventricular cardiac myocytes, the voltage-gated Na\(^+\) channels provide the positive inward current that depolarizes the ventricular myocyte. The entry of Na\(^+\) is rapid, as can be seen from the fast upstroke of the AP, which has been named phase 0, and is due in part to the kinetic characteristics of the voltage-gated Na\(^+\) channel, which shows rapid activation and rapid inactivation (Fig. 15.4). The membrane potential moves toward the Nernst potential for Na\(^+\), \(E_{Na}^+\). Phase 1 describes the notch in the AP that is seen at the initial reversal of the depolarization and is due to Na\(^+\) channel inactivation and the transient outward flow of K\(^+\) and inward flow of Cl\(^-\). However, at this time, complete repolarization is delayed due to the opening of L-type voltage-gated Ca\(^{2+}\) channels, allowing the influx of Ca\(^{2+}\) and resulting in a plateau of the AP, known as phase 2. At the plateau, the membrane potential is held near 0 mV for about 100 milliseconds, which leads to the activation of an outward K\(^+\) current. Phase 3 describes the termination of the AP and the repolarization of the cell with the outflow of K\(^+\) ions due to the opening of K\(^+\) channels contributing to the delayed rectifier K\(^+\) current. At phase 4, the cell has returned to its resting membrane potential, reestablishing its ion gradients with the activity of the Na\(^-\)K\(^-\)ATPase pump and the Na\(^-\)Ca\(^{2+}\) exchanger. Ionic channels and currents that work in concert to accomplish the cardiac AP and its cyclical automaticity have
highly complex organizational flows and structures that we are now beginning to understand. There are additional channels and mechanisms in the process of further investigation.

Given the importance of Na\(^+\) and K\(^+\) ion flow in the AP, any inborn or acquired defects in these channels may cause grave pathology. Over the past 20 years, multiple genes encoding for aberrant Na\(^+\) and K\(^+\) channels have been found to be responsible for inherited arrhythmias such as Brugada syndrome and long and short QT syndrome (4). These ion channel abnormalities, also known as cardiac channelopathies, can cause life-threatening arrhythmias such as ventricular tachycardia or fibrillation.

**AUTONOMIC CONTROL OF THE CARDIAC ELECTRICAL ACTIVITY**

The autonomic nervous system plays a major role in controlling the initiation of the heart beat and the rate of pacemaker firing. Both parasympathetic and sympathetic nervous inputs converge on the SA and AV nodal cells, exerting opposite influences on heart rate (5).

**Parasympathetic Nervous System**

The parasympathetic nervous system contributes nerve fibers from its cranial outflow through the cervical ganglia where preganglionic fibers course down to the cardiac plexus, and from there send postganglionic unmyelinated axons that impinge on the SA and AV nodal cells. The cardiac plexus is divided into a superficial and deep plexus; the superficial plexus is found at the base of the heart at the arch of the aorta, while the deep plexus is found on the anterior aspect of the trachea near its bifurcation. The parasympathetic fibers, carried by the vagus nerve, are cholinergic and release acetylcholine (ACh) when activated. ACh has three principal actions that result in the slowing of heart rate and a decrease in contractility: (a) activation of M2 muscarinic receptors in the SA and AV nodal cells, which (b) triggers a reduced spontaneous diastolic depolarization rate, which (c) reduces the slope of phase 0 of the AP, and thus results in a slower heart rate (5).

**Sympathetic Nervous System**

Sympathetic nervous input to the heart derives from preganglionic neurons in the upper four or five thoracic spinal segments. Axons pass to postganglionic neurons in thoracic and cervical ganglia. The cervical ganglia supply the superior, middle, and inferior cardiac nerves to the cardiac plexus, where they meet the thoracic cardiac nerves from the thoracic ganglia. Sympathetic nervous outflow then supplies the pacemaker cells in the SA and AV nodes, the conduction system, and both the atrial and ventricular myocytes. Norepinephrine, the major adrenergic synaptic mediator in the heart, activates specialized cardiac adrenergic receptors, the most important of which are the \(\beta_1\), \(\beta_2\) and \(\alpha_1\) receptors. Activation of \(\beta_1\) and \(\beta_2\) receptors leads to cardiac acceleration and increased contractility. Activation of the \(\alpha_1\) receptor also increases contractility. Table 15.1 illustrates the effects of adrenergic receptor activation.

**Figure 15.4** The ventricular cardiac myocyte action potential (AP). The numbers along the AP indicate the phases of the AP. The lower panel schematically represents the relative quantity and temporal relationship of the ionic movements involved in the AP.
$\beta$-Adrenergic stimulation additionally leads to increased activation of I$_{f}$ and accelerates diastolic depolarization, thus increasing the slope of phase 0 of the AP, so that a threshold is reached earlier. I$_{f}$ activation and repolarization are thus faster, with the net result more frequent firing of the AP and a faster heart rate (5). Recent work has focused on the primacy of Ca$^{2+}$ in regulating the pacemaker function of the SA node (6,7). When mechanoreceptors in the left and right atria sense increased venous return and resultant atrial stretch, an increase in sympathetic-mediated heart rate, known as the Bainbridge reflex, induces tachycardia in order to increase cardiac output (CO) and decrease intracardiac blood volume.

If both parasympathetic and sympathetic inputs to the heart are totally blocked, the heart rate actually increases due to the overriding parasympathetic inhibition seen in most individuals (5).

**CONTRACTION–RELAXATION CYCLE**

**Initiating Events**

The spontaneous and rhythmic electrical activity of the pacemaker cells must be transformed into regular and synchronized contraction and relaxation by the atrial and ventricular myocytes through a process described as excitation–contraction coupling. The electrical signal is uniformly passed through gap junctions from cardiac myocyte to cardiac myocyte, producing the AP. The unique characteristic of the AP essential for the initiation of the contractile process is the *plateau phase* (8). The plateau phase (Fig. 15.5) is due to the prolonged opening of the L-type Ca$^{2+}$ channel, which provides an inward positive current of Ca$^{2+}$, thus maintaining the depolarization for a prolonged period. The entry of Ca$^{2+}$ through the L-type channel initiates the sequence of events leading to contraction.

**Role of Calcium**

The Ca$^{2+}$ pump in the SR, known as the SERCA (sarcoplasmic reticulum calcium pump), transports Ca$^{2+}$ from the cytosol back into the SR. Together with the Na$^{+}$–Ca$^{2+}$ exchanger sarcolemmal protein, the SERCA sequesters Ca$^{2+}$ in the SR in anticipation of the excitation–contraction–relaxation process.

**Molecular Interactions**

Ca$^{2+}$ triggers the contractile process by interacting with the Ca$^{2+}$-binding protein, troponin C, which is an integral part of the sarcomere. The sarcomere is the smallest contractile unit and is defined from Z line to Z line (Fig. 15.6). The myofibrillar structure is made up of interacting filaments, termed thick and thin filaments. Thin filaments are polymers of actin monomers that are anchored to the Z line. The thick filament consists of myosin, a large protein made up of six subunits (Fig. 15.7). The thin filament consists of individual actin molecules that combine to form long polymer chains in a double helical array. Intereposred along the actin double helix are complexes of tropomyosin (Tm) and troponin (Tn) (Fig. 15.8). Tropomyosin is a linear molecule that lies in the groove of the thick filament, and Tn is found at the amino terminal end of the Tm molecule. Tn consists of a complex of three protein components: TnT, TnI, and TnC. Each of these components has a unique function essential for contractility. TnT contains the binding site for tropomyosin and allows the Tn complex to be bound to Tm. TnI is an inhibitory subunit. TnC is a molecular switch that undergoes Ca$^{2+}$-mediated conformational change and activates the actin–myosin interaction (9,10).
Characterizing the clinical picture. As shown in Figures 15.12, pressure–volume loops have been of great value in assessing the active and passive properties of the heart as a pump. The shape and position of the pressure–volume loops provide a graphic representation of the active and passive conditions of the heart. With that caveat in mind, specialized catheters, and manipulation of the different loads over the events of a single cardiac cycle (Fig. 15.9). As can be seen in Figure 15.10, pressure volume loops may be generated at different ventricular volumes, and the slope of the line connecting the point of end systole on a family of loops gives a measure of contractility. However, even this measurement of contractility has been shown to yield inconsistent results (11).

Currently, one invasive measure of contractility that appears most consistent is the preload recruitable stroke work (PRSW) relationship. First proposed by Sarnoff and Berglund in 1954 (14), PRSW has been proven to have a linear relationship to the end-diastolic volume (EDV) (15). This index measures contractility despite changes in preload and afterload. The PRSW is obtained from the integrals of a family of loops generated at different ventricular volumes, and the slope of the line connecting the point of end systole on a family of loops gives a measure of contractility. However, even this measurement of contractility has been shown to yield inconsistent results (11).

In clinical practice, pressure–volume loops are not routinely performed due to their time-consuming nature, need for specialized catheters, and manipulation of the different loading conditions of the heart. With that caveat in mind, pressure–volume loops provide a graphic representation of the active and passive properties of the heart as a pump. The shape and position of the pressure–volume loops have been of great value in characterizing the clinical picture. As shown in Figures 15.12 and 15.13, a particular pathologic state can be identified by the pressure–volume loop (20). The pressure–volume loop for patients with dilated cardiomyopathy and restrictive cardiomyopathy are markedly shifted to the right, while in hypertrophic cardiomyopathy, they are shifted to the left compared to normal individuals. Acute coronary ischemia also markedly alters the pressure–volume loops.

At the systemic level, the pressure–volume loop can be integrated over time by the eponymous Wiggers diagram of the cardiac cycle, as seen in Figure 15.14. The Wiggers diagram depicts the temporal relationship between cardiac flow and pressure changes, electrical activity, and auscultated heart sounds.

**Cardiac Contraction Cycle**

At the molecular level, contraction and force generation occur because of the interaction of the myosin head with actin (11). Two processes control contractility in the cardiac myocyte: the length of the sarcomere, and the intrinsic contractility of the contractile elements (12).

Positive peak $\frac{dP}{dt}$, the time differential of ventricular pressure, has been employed as a simple index of contractile function. While $\frac{dP}{dt}$ is a simple concept, it is technically challenging to obtain, and is clearly dependent on preload, afterload, and heart rate. A further measure of contractility is the end-systolic pressure–volume relationship (ESPVR) (13). The ESPVR is derived from the pressure–volume loop, an illustration of ventricular volumes plotted against ventricular pressures over the events of a single cardiac cycle (Fig. 15.9). As can be seen in Figure 15.10, pressure volume loops may be generated at different ventricular volumes, and the slope of the line connecting the point of end systole on a family of loops gives a measure of contractility. However, even this measurement of contractility has been shown to yield inconsistent results (11).

![Schematic representation of protein interactions comprising the contractile apparatus in the cardiac myocyte.](image)

**FIGURE 15.8** Schematic representation of protein interactions comprising the contractile apparatus in the cardiac myocyte. (From Ruegg JC. Cardiac contractility: how calcium activates the myofilaments. Naturwissenschaften. 1998;85:575; with permission.)

*FIGURE 15.9* The pressure–volume loop. The y axis represents the pressure in the left ventricle, while the x axis represents the volume in the ventricle. Systole begins with the closure of the mitral valve and initiation of isovolumic contraction at time A. The aortic valve opens at time B for ventricular ejection. Systole occurs from time A to time C, aortic valve closure. Following time C, there is isovolumic relaxation and mitral valve opening at time D, followed by ventricular filling until time A. Diastole occurs from time C to time A. (From Lewis AM. Cardiovascular physiology: flow-volume loops. In: Griffin B, ed. The Cleveland Clinic Cardiology Board Review. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013:37; with permission.)

*FIGURE 15.10* The pressure–volume loops in different ventricular volumes. The line connecting pressure–volume loops at end systole is a straight line called the end-systolic pressure–volume relationship. (From Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modification, and clinical use. Circulation. 1981;63:1223; with permission.)

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At the systemic level, the pressure–volume loop can be integrated over time by the eponymous Wiggers diagram of the cardiac cycle, as seen in Figure 15.14. The Wiggers diagram depicts the temporal relationship between cardiac flow and pressure changes, electrical activity, and auscultated heart sounds.
For the purposes of this text, we will focus on the left ventricle. At the beginning of ventricular systole, the electrical depolarization wavefront transmitted rapidly down the His-Purkinje fiber network, and represented by the R wave on the ECG, triggers the flood of incoming Ca$^{2+}$ to the actin–myosin complex, excitation–contraction coupling, and the subsequent increase in myocardial contractility to peak dP/dt. Once the left ventricular pressure increases to greater than that of the left atrium (6 to 12 mmHg), within 20 milliseconds, the mitral valve closes and its acoustic reverberations create S1, the first heart sound. The movement of the valvular annulus back towards the atrium is represented by the c wave followed by the x’ descent on the left atrial pressure waveform. On the pressure–volume loop, we observe isovolumic contraction as

![Pressure–Segment Length Loop](image)

**FIGURE 15.11** Pressure–segment length loop. In the inset, integrals of a family of pressure–segment length loops are plotted against end-diastolic segment length (EDL). The slope of this relationship, $M_w$, is a measure of contractility. (Adapted from Pagel PS, Kampine JP, Schmeling WT, et al. Comparison of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized chronically instrumented dog. Anesthesiology. 1990;73:278.)

![Pressure–Volume Loops](image)

both the mitral and aortic valves are shut but actin–myosin complexes continue to be recruited and ventricular pressure increases; isovolumic contraction is the first phase of systole.

Once the left ventricular pressure surpasses the aortic pressure threshold, the aortic valve opens and ejection begins. Note on both the pressure-volume loop and the Wiggers diagram that during this phase there are two separate slopes: An initial steep slope representing rapid ejection, as blood quickly exits the ventricle into the aorta, and a second, shallower slope representing delayed ejection as the SR takes up available Ca^{2+}, decreasing its availability for actin–myosin cross-bridging.

At the end of delayed ejection, the ventricular pressure will have fallen well below the aortic pressure, and the aortic valve closes. The end of the delayed ejection phase represents the end of systole. Closure of the aortic valve creates the first component of S2, the second heart sound. On Wiggers diagram, the left ventricular dicrotic notch represents a transient increase in aortic pressure and on the pressure-volume loop, we observe isovolumic relaxation since both mitral and aortic valves are again closed. Isovolumic relaxation is the first phase of diastole. Complete ventricular repolarization at this time is represented by the T wave on the ECG.
By comparing the end-systolic volume (ESV) to EDV on the pressure-volume loop, stroke volume of the ventricle and its derivative, the ejection fraction may be calculated. Average values for EDV, stroke volume, and ejection fraction are approximately 135 mL, 70 mL, and 50% to 55%, respectively.

As the ventricle relaxes and repolarizes, the left atrium has been filling with blood from the pulmonary veins. The corresponding increase in left atrial pressure is represented by the v wave on the left atrial pressure waveform. After complete ventricular relaxation, the pressure in the ventricle drops below the pressure in the left atrium, and the mitral valve opens. As the left atrial pressure drops, the v wave is followed by the y descent. Rapid or early filling subsequently occurs, contributing to approximately three-quarters of the ventricular filling. Atrial and ventricular pressures equalize during diastasis, with little net flow from one chamber to the other. Finally, the atrium undergoes its own depolarization and contraction, represented by the P wave on the ECG. Atrial systole, or the atrial kick, contributes the remaining one-quarter of the ventricular filling. On the left atrial pressure waveform, this is represented by the a wave followed by the x descent.

The electrical depolarization wavefront travels from the atrium down into the AV node and the His-Purkinje system, and the cycle restarts.

**BLOOD FLOW AND BLOOD PRESSURE**

**Basic Hemodynamic Models**

As stated above, the main purpose of the cardiovascular system is to circulate nutrient and oxygen-rich blood throughout the body and to remove its waste products for tissue homeostasis. The major vascular territories of the heart are noted in Table 15.2.

Any fluid that circulates within a closed system must conform to Newton’s laws of motion and fluid dynamics. These laws help us understand the principles of flow hemodynamics and can also be applied for our understanding of the cardiovascular system in both normal and abnormal conditions. Blood flow in the human body is in a constant state of flux, moving within areas that have different levels of resistance, pressure, and composition. For example, diseases such as anemia or polycythemia vera can change the hemoglobin content of blood, affecting its viscosity and thereby flow dynamics (Fig. 15.15).

Despite the fact that blood flow is not an ideal substrate for precise hemodynamic measurements, clinicians apply Newton’s hemodynamic laws to approximate systemic conditions and obtain data pertinent to patient care given the variability of blood flow (pulsatility, viscosity, and composition) and the frequent need for invasive monitoring.

**Cardiac Output**

One of the primary parameters used in clinical medicine to describe blood flow is CO, which is the total volume of blood pumped by the ventricle per minute, expressed in L/min (22). CO can be measured invasively via the Fick equation, tracer dilution methods and contour analysis or noninvasively by estimation of flow or ventricular volumes using echocardiography, cardiac magnetic resonance (cMRI), Doppler ultrasound, and other tools.

The CO can be defined mathematically as the product of two factors, the heart rate and stroke volume:

\[
CO = HR \times SV
\]

Physiologic changes affecting either the heart rate or stroke volume will have a direct impact on systemic CO. Stroke volume is defined as the difference between EDV and ESV, that is, the volume of blood ejected by the ventricle in each heart beat.

\[
SV = EDV - ESV
\]

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\[
SV = EDV - ESV
\]
Stroke volume is determined by preload, cardiac contractility, and afterload conditions of the heart.

- **Preload:** The wall pressure caused by the volume of blood in the ventricle at end diastole, usually reported as a volume or pressure, the left ventricular end-diastolic pressure (LVEDP).
- **Contractility:** The force of cardiac muscle contraction. Ejection fraction is a surrogate indicator of contractility.
- **Afterload:** The load in systole against which the ventricle has to contract to successfully eject blood, usually reported as a pressure-flow product, the systemic vascular resistance (SVR). SVR is a correlate of left ventricular afterload in the absence of valvular heart disease.

CO increases with exercise and body size (21). In population studies with latent coronary artery disease (CAD), CO has been shown to decrease with age (22). More recently, echocardiography and radionuclide studies in populations without CAD have shown that CO is maintained by compensating for a slower heart rate by increasing left ventricular EDV (23).

In clinical practice, CO is normalized for body surface area given the wide range of patient sizes that can be encountered, which is then labeled the cardiac index (CI). The CI is obtained by dividing the CO over body surface area (Table 15.3).

### Fick Principle and Mixed Venous Oxygen Saturation

The Fick principle, described in the late 1800s by the German physiologist Adolph Fick, was the first method used to calculate cardiac output. The principle states that the total uptake of a substance by an organ or tissue is equal to the product of blood flow to the organ and the arterial-venous concentration difference, or gradient, of the substance. The arterial-venous gradient is the total amount of substance supplied to an organ minus the amount leaving the organ. This mathematical relationship can be rearranged to solve for blood flow.

$$\text{Cardiac output} = \frac{\text{O}_2 \text{ consumption (mL/min)}}{\text{AV O}_2 \text{ difference}}$$

$$\text{Cardiac output} = \frac{\text{O}_2 \text{ consumption (mL/min)}}{(\text{systemic arterial O}_2 \text{ sat} - \text{mixed venous O}_2 \text{ sat}) \times 1.36 \text{ Hb} \times 10}$$

Oxygen consumption at baseline can be measured by oxygen uptake through a metabolic hood. This process is cumbersome and time consuming as it requires a tight-fitting gas exchange mask. In most cardiac catheterization laboratories an assumed oxygen consumption of 125 mL/min/m² is used to facilitate calculations. Mixed venous oxygen saturation (MVO₂) is obtained by drawing a sample of blood from the distal port of a pulmonary artery catheter.

All invasive and noninvasive methods of CO measurement have limitations and pitfalls of which practitioners need to be aware. CO by the Fick Method can have significant error in the presence of intracardiac shunts or in nonsteady states (i.e., the critically ill). The assumed Fick equation estimates oxygen consumption based on patient weight instead of direct measurement, however this estimation can introduce significant error into the results. In a best case when using the assumed Fick equation, the error associated with measuring CO will be about 10% to 15%. Under less stringent conditions this variation can rise significantly (23). The Fick

### Table 15.3 Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>70–105 mmHg</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>90–140 mmHg</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>60–90 mmHg</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>0–5 mmHg</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure</td>
<td>10–20 mmHg</td>
</tr>
<tr>
<td>Systolic pulmonary pressure</td>
<td>15–25 mmHg</td>
</tr>
<tr>
<td>Diastolic pulmonary pressure</td>
<td>5–10 mmHg</td>
</tr>
<tr>
<td>Capillary wedge pressure</td>
<td>5–12 mmHg</td>
</tr>
<tr>
<td>Cardiac index (CI)</td>
<td>2.5–3.5 L/min/m²</td>
</tr>
<tr>
<td>Stroke volume index (CI/heart rate)</td>
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</tr>
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<td>Systemic vascular resistance index</td>
<td>1,200–1,500 dyne-sec/cm⁻²/m²</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index</td>
<td>80–240 dyne-sec/cm⁻²/m²</td>
</tr>
</tbody>
</table>

**Figure 15.16** Major factors affecting cardiac output, divided by those primarily influencing the heart rate and those primarily influencing the stroke volume. (Valvular heart disease not included.)
method is the most accurate method for CO measurement in low CO states due to the large differences encountered in arterial and mixed venous oxygen saturations, thereby reducing errors in measurement of oxygen saturation (24,25).

Other invasive methods to measure CO such as the indicator dilution or thermodilution method can have significant error in low CO states, arrhythmias, or severe tricuspid regurgitation. The indicator dilution method is most accurate in high output states.

Deoxygenated blood returning to the heart through the inferior and superior vena cava and coronary sinus will have different oxygen saturation levels due to the oxygen consumption ratios of tissues and organs. Inferior vena cava saturation is usually higher than superior vena cava saturation due to renal blood flow and lower oxygen extraction by the kidneys. Coronary sinus oxygen saturation is very low due to high myocardial oxygen extraction ratios but its systemic contribution is negligible due to its small volume. Normal pulmonary artery oxygen saturation (mixed venous O2 saturation) is 70% to 75% as the normal tissue oxygen extraction is usually in the 25% to 30% range in humans.

In critical illness or in states of increased metabolic demand, tissue oxygen extraction increases throughout the body. In response, regulatory centers will attempt to maintain homeostasis by increasing oxygen delivery to tissue through an increase in cardiac output. MVO2 can therefore be used as a surrogate marker for cardiac output, as it is decreased in low CO states such as congestive heart failure and can be severely decreased in cardiogenic shock. Isolated interpretation of MVO2 should be done cautiously, as we know based on Fick’s equation that MVO2 can also be decreased in severe anemia and hypoxemia without a significant decrease in cardiac output.

Other applications of oxygen saturation in cardiovascular disease are in the diagnosis of intracardiac shunts. Measurement of oxygen saturations in various locations within the right heart chambers and vessels, termed an oxygen saturation run, can be diagnostic for clinically significant shunts such as ASD, VSD, and others (26). A significant increase or “step up” in oxygen saturation levels is noted in intracardiac shunts.

Frank-Starling Law

The Frank-Starling law states that the preload, the pressure associated with the maximal length to which myocardial cells are stretched at the end of diastole, will determine the active tension they develop when stimulated to contract. The Frank-Starling law is an intrinsic property of myocytes and is not dependent upon extrinsic nerves or hormones.

In the 1980s, Otto Frank studied isolated frog heart muscle and found that the strength of ventricular contraction increased when the muscle was stretched prior to contraction. Subsequent work by Ernest Starling in dogs also showed that increasing venous return and therefore preload also increased contractility. Conditions that increase preload cause an increase in cardiac contractility and thereby stroke volume, ultimately increasing cardiac output. Contractility increases linearly with sarcomere length up to a point, the limit beyond which there is no further increase in contractility and an actual decline in contractile strength can occur if further dilated.

Ohm’s Law

Ohm’s law of electron flow states that the current or flow between two points is proportional to the resistance between the two, so that the greater the resistance the lower the current or flow. Although in the strictest sense this law only holds true for a closed electrical circuit, it has been successfully applied to cardiovascular physiology.

\[ I = \frac{V}{R} \]

\[ \text{Flow (Q)} = \frac{\text{pressure gradient (∆P)}}{\text{resistance (R)}} \]

In order for blood flow to occur within the body, a pressure gradient must exist between two points. Blood will always flow from a high pressure region to a lower pressure region, such as from the left ventricle to aorta, aorta to cerebral circulation, or veins to right atrium. Flow is inversely proportional to vessel wall resistance.

Ohm’s law is primarily used to calculate vascular resistance in patients in whom blood flow (by means of a pulmonary artery catheter) and blood pressure (by means of an arterial catheter) are measured simultaneously. In clinical practice, the SVR is calculated from the CO, the mean arterial blood pressure (MAP), and the central venous pressure (CVP):

\[ \text{SVR} = \frac{(\text{MAP} - \text{CVP})}{\text{CO}} \]

Likewise, pulmonary vascular resistance (PVR) is calculated from the cardiac output, the mean pulmonary artery pressure (PAP Mean), and the pulmonary capillary wedge pressure (PCWP). The latter is measured after balloon occlusion of a branch of the pulmonary artery and is normally in equilibrium with left atrial pressure:

\[ \text{PVR} = \frac{(\text{PAP Mean} - \text{PCWP})}{\text{CO}} \]

Poiseuille’s Law

Resistance to blood flow is another important physiologic variable, one that constantly changes in response to external and internal factors. The resistance (R) to laminar flow through a rigid tube can be expressed by Poiseuille’s law, which states that resistance depends on both the composition of blood and the properties of blood vessels, including length (L) and radius (r) of the vessel.

\[ R = \frac{8\eta L}{\pi r^4} \]

Specifically, the viscosity (η) increases with hematocrit and with plasma protein concentration (see Fig. 15.15), whereas the radius of blood vessels is under tight control by the autonomic nervous system. Poiseuille’s law gives only an approximation of the true hemodynamic resistance because the human circulation deviates in many ways from the conditions under which the law applies. Blood vessels are not rigid and instead form branching and tapering elastic tubes; blood flow is not steady but pulsatile; flow is not necessarily laminar, but has turbulent flow components at certain locations.

Among the three independent variables of Poiseuille’s law, the radius of blood vessels is capable of undergoing the most significant change. Total vessel radius, adjusted by a fine balance between vasodilation and vasoconstriction, is the main regulator of vascular resistance. SVR is the net result of the
resistance generated by many vessels arranged both in series and in parallel.

Arterioles, in particular, are the main targets of the various regulatory mechanisms that lead to vasodilation or vasoconstriction. Because the resistances of the coronary, cerebral, and renal circulations are primarily controlled by local demand, the main factor that regulates total SVR is the net radius of arterioles in muscles, skin, and the gut.

Systemic arteries expand temporarily during systole, a mechanism that is used to store potential energy. Systemic veins and all pulmonary vessels expand and contract in order to accommodate changes in circulating blood volume. The degree to which vessels can expand is defined by their compliance (C):

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

where \(\Delta V\) is the change in volume that corresponds to a certain change in transmural pressure, \(\Delta P\), the pressure difference between the inside and the outside of the vessel. The compliance is high in systemic veins and the pulmonary vasculature, which is why changes in blood volume will primarily affect the volume of these structures. In contrast, compliance is low in systemic arteries; as a result, their total volume is relatively stable, and they distend only minimally when the arterial pressure rises during systole. Compliance is inversely related to resistance; measurements have shown that SVR is normally about 10 times higher than the PVR (see Table 15.3).

In a steady state, blood flow is equal at any two cross sections in series along the circulation. Thus, the flow through the aorta equals the flow through all of the systemic capillaries. Although the aorta is the largest blood vessel, the combined cross-sectional area of the capillaries far exceeds the aortic cross section. As a result, the velocity of flow is much lower in the capillaries than in the aorta.

**Laplace’s Law**

Laplace’s law, first described in the 1700s, helps us understand the importance of vessel wall thickness as a compensatory mechanism of concentric versus eccentric ventricular wall hypertrophy in cardiomyopathies.

\[
\text{Wall tension} = \text{pressure} \times \frac{\text{radius}}{\text{wall thickness}}
\]

Laplace’s law assumes that tension in the wall of a hollow cylinder is directly proportional to the cylinder’s radius and the pressure across the wall caused by flow inside. Therefore, with luminal dilatation and increasing radius, wall tension will increase exponentially. For a similar level of blood pressure, large arteries that have an increased radius must have thicker walls when compared to smaller arteries so as to withstand the levels of wall tension. In an aortic aneurysm, in which the vascular wall is dilated, the process predisposes to an inescapable cycle where increases in wall tension potentiate further weakening of vessel walls, culminating in subsequent rupture.

In the left ventricle, conditions that typically increase ventricular afterload, such as hypertension or aortic stenosis, cause an increase in ventricular wall and cavity tension due to pressure overload. This pressure overload, over time, causes a pattern of concentric ventricular hypertrophy without an increase in ventricular radius. Dilated cardiomyopathies, however, typically cause a volume overload of the left ventricle with an increase in ventricular wall radius and tension. This increase in wall tension induces a compensatory increase in ventricular wall thickness of eccentric hypertrophy. This increase in muscle mass compensates for wall tension but also leads to an increase in oxygen consumption secondary to increased tissue requirements needed to generate the same blood pressure as in normal physiological states.

**Generation of Blood Pressure**

Although blood pressure is a poor indicator of CO and adequate tissue perfusion, it is still one of the two key measurements in cardiovascular hemodynamics alongside heart rate.

The pressure of the systemic circulation is produced by ejection of blood from the left ventricle. As a result of this ejection, blood is accelerated, and the elastic walls of the central blood vessels are slightly distended. This distension is crucial for normal circulatory function because it stores potential energy in vascular structures, resulting in a continuous flow of blood even after the actual ejection period is completed. Although the pressure during the ejection period (systolic blood pressure) is higher than the pressure after the ejection period (diastolic blood pressure), elastic recoil sustains the flow of blood at all times.

The difference between systolic and diastolic blood pressure is called pulse pressure. Pulse pressure is determined by the stroke volume and arterial compliance. A wide or increased pulse pressure can be seen in conditions that primarily increase systolic blood pressure or lower diastolic blood pressure. Conditions that increase systolic blood pressure do this by increasing stroke volume or decreasing arterial compliance (isolated systolic hypertension, old age with loss of arterial elastance and hyperkinetic states). Conditions that decrease diastolic blood pressure are severe aortic insufficiency, AV fistula, septum, and vasodilated states. A narrow pulse pressure is usually seen in conditions with low CO such as cardiogenic shock, cardiac tamponade, hemorrhage, or trauma. Although not well defined, normal values for pulse pressure are in the range of 30 to 40 mmHg.

An important indicator of the driving force of the circulation is the MAP. The MAP of one cardiac cycle is the area under the blood pressure curve (\(\int P \, dt\)) divided by the time of the cardiac cycle (\(\Delta t\)):

\[
\text{MAP} = \frac{\int P \, dt}{\Delta t}
\]

Determination of MAP by this equation requires invasive monitoring of a continuous blood pressure tracing. When blood pressure is measured by noninvasive techniques, MAP can be approximated from diastolic (DBP) and systolic (SBP) blood pressures by the following equation:

\[
\text{MAP} = \frac{[2 \times \text{DBP} + \text{SBP}]}{3}
\]

We also need to remember the noninvasive MAP formula is best applicable at lower heart rates approaching 60 beats per minute, as we are assuming a normal diastolic interval which is usually twice that of systole. When the heart rate increases, diastolic time decreases and the accuracy of the formula will decrease.

The MAP changes very little between the aorta and the small arteries. However, in arterioles and capillaries, a large pressure gradient exists, which eventually dissipates the mean pressure to a venous pressure value near zero. Despite the
Distribution of Blood Volume

The circulating blood volume in adults is 60 to 70 mL/kg for women and 70 to 80 mL/kg for men. In neonates, the blood volume is 80 to 90 mL/kg. More than half of the blood volume is present in the venous system, including veins, veins, and the cava (Table 15.4). As discussed above, the compliance of veins is about 10 times higher than that of systemic arteries. Thus, small changes in venous pressure are associated with large changes in venous volume, and the venous system serves as a reservoir to accommodate shifts in total blood volume.

Stroke volume and CO are highly sensitive to the degree of filling of the cardiac ventricles. Cardiac filling in turn depends on the central blood volume, which is defined as intrathoracic blood present in the heart, cava, pulmonary circulation, and intrathoracic arteries. The distribution of blood between the central (intrathoracic) compartment and the peripheral (extrathoracic) compartment can change with body position and with sympathetic tone. Redistribution of blood occurs mainly between compliant structures, such as the heart, the veins, and the pulmonary vasculature. The variable portion of the peripheral blood volume is located in the veins of the extremities and the abdominal cavity. In contrast, the blood volume in systemic arteries changes very little because of their low compliance. Changes in CVP can be used as an indicator of changes in central blood volume. Although this technique is widely employed in the practice of critical care, it is not very sensitive, and it is only accurate if a number of preconditions apply, such as normal cardiac function, normal intrathoracic pressures, and accurate positioning of the pressure transducer.

Just like the vascular resistance, blood volume and blood distribution are under endocrine and autonomic nervous control. Angiotensin II and aldosterone decrease renal excretion of sodium, which leads to an increase in total plasma volume. Atrial natriuretic peptide is released into the bloodstream when atria are stretched, causing increased renal sodium excretion, which therefore leads to a decrease in plasma volume. Erythropoietin is a hormone released by the kidneys that causes bone marrow to increase the production of red blood cells, which also increases total blood volume. The distribution of blood volume is sensitive to the sympathetic tone. High sympathetic outflow causes vasoconstriction in addition to the constriction of arterioles. The main effect of vasoconstriction is an increase of the central blood volume at the expense of the peripheral blood volume.

Table 15.4 Distribution of Blood Volume

<table>
<thead>
<tr>
<th>Element of Circulation</th>
<th>Blood Volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arteries</td>
<td>10–12</td>
</tr>
<tr>
<td>Systemic capillaries</td>
<td>4–5</td>
</tr>
<tr>
<td>Systemic veins</td>
<td>60–70</td>
</tr>
<tr>
<td>Pulmonary circulation</td>
<td>10–12</td>
</tr>
<tr>
<td>Heart</td>
<td>8–11</td>
</tr>
</tbody>
</table>

Key Points

- Blood flow in the human body is not a substrate that lends itself to precise or easy hemodynamic monitoring. In spite of this, clinicians can still apply Newton’s laws of flow dynamics in order to obtain pertinent information and measurements that can be used clinically at bedside.
- Frank-Starling law states that cardiac preload, the pressure to which myocardial cells are stretched at the end of diastole, will influence cardiac contractility and therefore the stroke volume of the heart.
- Ohm’s laws state that blood flows from a high pressure area to a lower pressure area and that flow is inversely proportional to vessel wall resistance.
- Poiseille’s laws state that vessel radius, vessel length, and blood viscosity determine resistance to blood flow within the vessel. Of these, vessel radius being the most significant.
- Laplace’s laws state that the larger the vessel radius the larger the wall tension required to withstand a given internal fluid pressure.

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References


