ANATOMY AND DEVELOPMENT

Anatomy

In the normal heart, the systemic (superior and inferior vena cavae) and cardiac veins (via the coronary sinus) empty into the right atrium (RA). The RA is defined by its broad and blunt appendage with the pectinate muscles extending beyond the appendage to the crux of the heart. The morphologically normal RA also contains the limbus of the fossa ovalis, the sinus node, and the triangle of Koch, through which the conduction fibers run to the atrioventricular (AV) node.

The left atrium (LA) is the most posterior of all the cardiac chambers. Unlike the RA, the LA does not have pectinate muscles extending out of its fingerlike appendage, and thus it has a smooth interior. The LA receives the pulmonary venous return from the lungs, usually through 4 separate veins that drain into the posterior portion of the atrium.

Between the atria is the interatrial septum, made up of remnants of the septum primum and septum secundum, which remains as the valve of the fossa ovalis. The septum primum is an LA structure that can be seen behind the limbus when looking from the RA side. The limbus represents the septum secundum and is the RA portion of the septum. The limbus and the valve should eventually fuse together; however, when this does not occur, a patent foramen ovale persists.

When there are 2 AV valves and 2 ventricles, the tricuspid valve is always associated with the right ventricle (RV). The 3 leaflets are the septal, inferior, and the anterior leaflets. Papillary muscles support the zones of apposition between the leaflets, with chordal attachments between the septal leaflet and the ventricular septum. These septal attachments, along with a slight apical displacement, help distinguish a morphological tricuspid valve from a mitral valve. The normal mitral valve has an anterior leaflet and a posterior leaflet. In contrast to the tricuspid valve, which has diffuse attachments of the chordae, the mitral valve chordae attach to 2 distinct papillary muscles.

A morphological RV is the more anterior ventricle and is tripartite, consisting of an inlet, a body, and an outlet. The free wall is relatively thin compared with that of the left ventricle (LV), and the endocardium is heavily trabeculated. A moderator band is seen toward the apex. The inlet valve of the RV is more apically displaced than the left-sided AV valve. The outlet of the RV is smooth and entirely muscular, referred to as either conus or infundibulum.

The LV only has 2 parts, an inlet and an outlet, separated by the anterior leaflet of the mitral valve. The mitral valve is in fibrous continuity with the aortic valve at the outlet. The apex has only fine trabeculations and has a much smoother appearance to its endocardial surface. The free wall of the LV is much thicker than that of the RV. The inlet of the LV, the mitral valve, has a more superior insertion into the septum, and thus there is a small component of the LV that shares a septum with the RA. Unlike the outlet of the RV, the outlet of the LV has no conus in the outflow region.

In sum, the ventricles can be differentiated most reliably by identifying the type of AV valve guarding the inlet, the presence or absence of continuity between that valve and the semilunar valve, and the presence of trabeculations and a moderator band.

The ventricular septum divides the LV from the RV but also has a small portion that separates the RA from the LV. This septum has 4 components: inlet, trabecular, outlet, and membranous septum. The inlet portion is the most posterior and separates the tricuspid and mitral valves. The trabecular portion is the largest, extends to the apex, and divides the heavy trabeculations in the right from the fine trabeculations in the left. This, plus the outlet portion, makes up the muscular portion of the septum, with the outlet portion dividing the right and left ventricular outflow tracts. The membranous portion of the septum is
the smallest component and sits in the Y of the trabecula septomarginalis halfway between the tricuspid and pulmonary valves.

The outlets of both ventricles are guarded by the trileaflet semilunar valves. They maintain unidirectional flow by opening and closing passively, without any chordae or papillary muscles. The pulmonary valve is more rightward and anterior, crossing in front of the proximal ascending aorta before branching into the right and left pulmonary arteries. The aortic valve is a midline structure, located posterior and leftward of its counterpart. The ascending aorta passes in front of the right pulmonary artery before coursing leftward and giving off the head and neck vessels. The normal left arch then crosses over the left main bronchus (which is how arch-sidedness is defined) with the descending aorta running behind the left pulmonary artery.

The structures of the heart are supplied by the coronary arteries, originating from the aortic sinuses. The right coronary artery (RCA) and the left main coronary artery (LCA) come off the so-called right and left sinuses, respectively. The RCA runs in the right AV groove around to the crux of the heart posteriorly, supplying the RV and most of the diaphragmatic surface of the ventricular mass. The conal artery either is the first main branch or has a separate origin from the right cusp, supplying the RV outflow conal area. The conal artery also can send an early branch to the sinus node. Posteriorly, at the crux of the heart, the conal artery sends a branch to the AV node and supplies the posterior descending artery (this defines right dominance of the coronary arteries).

The LCA exits the aortic sinus and enters the margin of the transverse sinus before branching into the left anterior descending artery and the left circumflex artery. The LCA is larger than the RCA, as it supplies more myocardial mass, including most of the LV and muscular interventricular septum. The left anterior descending artery traverses anteriorly down the interventricular groove, giving off the diagonals and the septal perforator arteries, and may extend as far as the posterior interventricular groove. The left circumflex artery runs in the left AV groove and either terminates as the obtuse marginal artery or, in 10% of the population, continues all the way posterior to supply the posterior descending artery (making the coronary supply left-dominant). The majority of the larger cardiac veins drain into the coronary sinus, a remnant of the left horn of the systemic venous sinus. This runs in the posterior groove of the left AV junction, draining into the RA.

**Development**

The heart tube is formed by day 19 of gestation and begins to loop, beat, and form primitive chambers within the next few days. It contains the precursors to the cardiac segments. Segmental differentiation creates the physiologic competence of the embryonic heart, including unidirectional antegrade blood flow. The newly formed heart tube may be divided into regions (*Figure 1, Table 1*).

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**Figure 1. Embryonic heart tube and “D looping”**

The heart tube is formed by day 19 of development and begins beating within days. The arterial pole is the cranial portion of the heart tube, developing ultimately into the great vessels. The venoatrial pole, located caudally, will become the atria and form part of the venous system returning blood to the atria.
Embryologic Abnormality Correlating Cardiac Defect

Anterior deviation of conal septum, overriding aorta

Persistent left-sided conus, failure of outflow septation

Failure of truncal cushions to spiral, incorrect great vessel septation

Failure of neural crest cell migration, lack of outflow septation, and incomplete great vessel septation

Incomplete septation of the great vessels

Tetralogy of Fallot

Double-outlet right ventricle

D-transposition of the great arteries

Truncus arteriosus

Aortopulmonary window

Table 1. Embryonic Structures and Mature Cardiac Segments

<table>
<thead>
<tr>
<th>Embryonic Structure</th>
<th>Mature Cardiac Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus venosus</td>
<td>Smooth part of right atrium (sinus venarum), coronary sinus, oblique vein of left atrium</td>
</tr>
<tr>
<td>Primitive atrium</td>
<td>Trabeculated parts of right and left atra</td>
</tr>
<tr>
<td>Primitive ventricle</td>
<td>Trabeculated parts of right and left ventricles</td>
</tr>
<tr>
<td>Bulbus cordis</td>
<td>Smooth part of right ventricle (conus arteriosus), smooth part of left ventricle (aortic vestibule)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>Aorta, pulmonary trunk</td>
</tr>
</tbody>
</table>

Normal right looping or D-looping occurs as the veno-atrial pole comes up behind the arterial pole with the embryonic ventricle and bulbus cordis looping out to the right. Once the heart loop has formed, the primitive RV (caudal portion of bulbus cordis) and LV (embryonic ventricle) remain connected with a narrowing in between that is called the primary interventricular foramen. In the early portion of this stage, the heart is essentially a double-inlet LV with double-outlet RV. For the heart to become a 4-chambered heart with series circulation, septation must occur correctly.

Early on, the AV canal is committed to the embryonic ventricle or the future LV. For normal inlets to both ventricles to develop, this canal must shift to span the interventricular foramen. Once the AV canal is committed to both ventricles, septation begins with development of cushion tissue. The superior and inferior endocardial cushions grow together medially and separate the canal into a right- and left-sided channel.

Conotruncal cushions also form in a somewhat similar method to separte the ventricular outflows and divide the truncus arteriosus into separate great vessels. The difference here is that these cushions include neural crest cells (so conotruncal defects tend to be associated with craniofacial defects, such as DiGeorge syndrome) and have to twist to separate the great vessels correctly. Congenital cardiac defects associated with conotruncal cushions are listed in Table 2.

Once the cushions have septated inflows and outflows correctly, the chambers still need further septation to be completely separated. In the common atrium, this occurs with the formation and regression of septal tissue. Initially, an invagination of the roof of the common atrium grows into the lumen, to ultimately fuse with the fused endocardial cushions; failure of the endocardial cushions to fuse appropriately means that the septum primum cannot appropriately fuse, thus the association of primum atrial septal defect (ASD) with atrioventricular septal defect (AVSD). As this fusion occurs, perforations form in the upper portion of the septum primum forming the ostium secundum (by way of which the oxygenated blood from the umbilical vein is able to get across the septum prenatally). A second infolding of the roof of the atrium occurs to the right of the previous septum primum but does not completely separate the atra. This forms the limbus of foramen; the remains of the septum primum form the valve of the foramen. If the septum secundum is insufficient (or the septum primum is excessively resorbed), a secundum ASD will be present.

The ventricles form separate chambers after fusion of the endocardial cushions. The muscular portion of the septum forms by fusion of the medial walls of the primitive ventricles. As the conus septum is completely formed, the interventricular foramen becomes smaller and is ultimately
closed by an outgrowth of tissue from the inferior endocardial cushion. This tissue becomes the membranous septum by growing into the muscular septum and fusing with the conus septum. Given this sequence of events, it is easy to see why the most common ventricular septal defect (VSD; and the most common congenital heart defect overall) is failure of fusion of the outgrowth, forming a so-called perimembranous VSD.

Once the endocardial cushions fuse, the AV valves form. Incomplete delamination of the septal leaflet of the tricuspid valve results in Ebstein anomaly. The semilunar valves form after partitioning of the truncus arteriosus is nearly complete.

Pulmonary veins are formed from outpouchings of the lungs themselves that form a splanchnic plexus. This plexus coalesces and forms a common vein that finds the back of the LA, ultimately becoming absorbed into the back of the LA so that each of the pulmonary veins drains separately into the chamber. Failure of any of these veins to join this plexus will result in partial anomalous pulmonary venous return, and failure of the common vein to join the LA will result in total anomalous pulmonary venous return.

Prior to extrauterine life, the lungs do not function to oxygenate blood; only 5% to 10% of combined cardiac output goes through this circuit. The ductus arteriosus (DA) is essential to fetal life, allowing blood from the RV (deoxygenated blood) to bypass the highly resistant lungs and continue to the low-resistance placenta for oxygenation and removal of waste products. The patency of the DA prenatally is maintained by low fetal oxygen tension and circulating prostaglandins (prostaglandin E₂ and prostacyclins (prostacyclin I₂). At delivery and with the first inspiration into the lungs, the oxygen tension increases, stimulating factors to cause muscular contraction of the DA. Combined with decreased prostaglandin E₂ and prostacyclin I₂, this leads to functional closure of the DA within minutes to days of life.

**MYOCARDIAL MECHANICS**

**Sarcomere Function**

*Excitation-Contraction Coupling*

Excitation–contraction coupling is the process of myocyte contraction, beginning with an action potential and finishing with binding of calcium to troponin C (TnC). Calcium (Ca²⁺) is an important modulator of cardiac function (see also Chapter 3). An action potential depolarizes the sarcolemma of a myocyte, stimulating the voltage-gated Ca²⁺ channels (L-type channels) to open and allow plasma Ca²⁺ to enter the cytoplasm of the myocyte. This increase in Ca²⁺ concentration prompts the sarcoplasmic reticulum (SR) via the ryanodine receptors to release its stores of Ca²⁺ into the cytoplasm, a process termed *calcium-induced calcium release*. The rapid increase in Ca²⁺ serves 2 functions: (1) It binds to SR channels to stop the continued release of Ca²⁺, and (2) it binds to TnC to complete the process of excitation–contraction coupling. Cytosolic Ca²⁺ levels are returned to baseline with reuptake into the SR via the SR calcium-adenosine triphosphatase pump and by removal across the sarcolemma to the extracellular plasma via the sodium-calcium exchanger.

The basic contractile unit of cardiac muscle is the sarcomere ([Figure 2](#)). The sarcomere is made up of several

**Figure 2. A sarcomere broken down into its structural components**

Sarcomere thin filament proteins are composed of actin and troponins C, T, and I. Sarcomere thick filament proteins include myosin heavy chain, myosin essential and regulatory light chains, myosin-binding protein C, and titin. The sarcomere is anchored through titin and actin interactions with Z-disc proteins.

contractile proteins, including myosin, actin, tropomyosin, troponin complex, and titin. The individual sarcomeres are connected and defined at either end by the Z disk. These proteins are related in such a way to form the thin filaments and the thick filaments of the sarcomere.

The thin filaments of the sarcomere are composed of actin, tropomyosin, and the troponin complex, with actin forming the backbone of the filament. The thin filament is anchored to the Z disk at one end and overlaps the thick filament at the other end. The thin filaments on either side of the Z disk are referred to as the I band. Tropomyosin proteins wrap around actin in a helical fashion, with the ends of each protein overlapping its neighbor. In the basal state (diastole), tropomyosin is attached to actin in such a way as to cover the sites that the myosin heads of the thick filament can attach. The troponin complex is made up of 3 separate proteins, T, I, and C. The entire complex wraps around actin as does tropomyosin, following the same path. Troponin T (TnT) binds the complex to tropomyosin and can be thought of as the glue that holds all the components of the thin filament together. Troponin I (TnI) inhibits any interaction between actin and myosin, binding to actin in diastole. Troponin C (TnC) is the end target of those increased intracellular concentrations of Ca\(^{2+}\) that result from excitation-contraction coupling. When TnC binds Ca\(^{2+}\), tropomyosin moves and exposes those binding sites for the myosin head, allowing cross-bridging to occur between the thick and thin filaments, causing contraction of the sarcomere.

Myosin and titin make up the thick filaments of the sarcomere. The portion of the sarcomere consisting of the thick filament is the A band. The ends of the thick filament overlap the thin filaments; the central area that is thick filament only contains the M line. Titin is a large protein that is not thought to be contractile but merely keeps the other filaments aligned. Myosin is the most prevalent contractile protein in the sarcomere, made up of both light chains and heavy chains. The heavy chain tails wrap together to form the bulk of the thick filament, whereas the heads project out to form the cross-bridges.

When increased levels of cytosolic Ca\(^{2+}\) bind to TnC, tropomyosin moves away from the binding sites on actin, thus allowing for the creation of cross-bridges between the myosin head and actin. The rate of force development depends on the extent to which the thin filament is activated by Ca\(^{2+}\). Relaxation (diastole) occurs when Ca\(^{2+}\) is decreased in the cytosol.

**Length-Tension Relationship**

The Frank-Starling relationship states that ventricular stroke volume depends on preload; that is, the more blood that is in the ventricle at end-diastole, the more that is pumped out of the heart with that contraction. At a molecular level, this is explained by the overlap of the myofilaments (thick and thin) and sensitivity to Ca\(^{2+}\). The longer the sarcomere length (up to a point), the more sensitive the myofibrils are to Ca\(^{2+}\), and this is what leads to increased tension development for increased sarcomere length.

**Integrated Muscle Function**

**Pressure-Volume Relationship**

The relationship between instantaneous pressure and volume in the ventricle forms a counterclockwise loop through one complete systole-diastole cycle (Figure 3) that represents the external work of that ventricle. The diagram is roughly a rectangle, with the base representing diastolic filling of the ventricle. An increased slope of this line indicates increased stiffness of the ventricle, requiring higher filling pressures to achieve the desired volume. The right lower corner represents end-diastolic volume (EDV) (preload) and pressure (lusitropic state). Isovolumic contraction begins here, with the normal loop shooting straight up until it exceeds the afterload (aortic pressure). Only after the ventricle reaches its afterload pressure does it begin to eject blood into the aorta. The top of the rectangle represents the ejection phase of the ventricle, with the shape of this line depending on the afterload as determined (mostly) by peripheral arterial resistance. Systole ends at the top left corner, and this end-systolic pressure-volume relation represents the contractility of the ventricle. This point is pushed up and to the left by a positive inotropic agent and down and to the right by a negative inotropic agent. When a series of loops are plotted for an individual ventricle at different preload and afterload states, connecting the respective end-systolic points with a line forms a quantitative representation of contractility. The slope of this line is the end-systolic elastance (E\(_s\)), an index of contractility that reflects the increased stiffness of the ventricle that occurs with the increased number of myofilament cross-bridges.

The loop is completed after end-systole with isovolumic relaxation. The ventricle begins to fill again after this pressure falls below atrial pressure, and the cycle is repeated.

Much in the way that E\(_s\) and contractility can be calculated by plotting the end-systolic points, vascular elastance (E\(_v\)) is represented by the slope of the line that connects the end-systolic point on the loop with the EDV on the x-axis. Further discussion of these concepts is given in Figure 4.
Figure 3. Normal left ventricular pressure-volume loop

One counterclockwise loop traces an entire cardiac cycle. Beginning with the right lower corner, the end-diastolic pressure and volume correspond to ventricular preload. As isovolumic contraction occurs up the right side of the loop, the volume stays constant until the ventricular pressure exceeds afterload and ejection occurs, as seen across the top of the loop. Pressures remain elevated as ventricular volume decreases, until the end of contraction is reached as indicated at the top left. This represents the end-systole point, which can be used to determine an index of contractility, the end-systolic elastance. With contraction complete, the semilunar valve closes and ventricular pressure decreases while volume remains constant during isovolumic relaxation. As the ventricular pressure drops below atrial pressure, ventricular filling begins along the bottom of the loop.

Figure 4. Pressure-volume loops and stroke volume (SV)

(A) Changes in afterload. Center loop shows a normal left ventricular curve. Increasing systemic vascular resistance results in striped loop, with a decrease in SV. Decreasing afterload results in solid-fill loop, with a flatter ejection curve and increase in SV. Variability in afterload is also shown in the schematic, with striped loop requiring increased preload and solid loop requiring decreased preload compared to baseline. (B) Elastance (E\text{es}; an index of contractility) as determined by a series of pressure-volume loops, generated for a normal ventricle (striped loop) by varying the preload. Connecting the end-systole points on each of these loops forms a line, the slope of which is E\text{es}. The steeper the slope, the better the contractility of that ventricle. (C) Effect of change in contractility, or E\text{es}, on the SV of the ventricle. Striped loop represents the normal ventricle pressure-volume loop with baseline E\text{es}. Increasing the slope of the line yields increased end-systolic pressure and stroke volume for the same preload and afterload. (D) Vascular elastance (E\text{a}) as determined from pressure-volume loop. The slope of a line drawn from the end-systole point to the x-intercept of the end-diastolic volume represents E\text{a}, with a steeper line indicating increased elastance.
Clinical examples of pressure-volume loops are described in Chapter 8.

**Preload**

The cardiac function curve shows how changes in central venous pressure (CVP) or EDV, both indicators of venous return (preload), affect cardiac output (CO). As venous return approaches zero, CO also approaches zero. As venous return increases, the curve slopes up at a rate dependent on variables including afterload and contractility. Ultimately, increases in venous return no longer augment CO, and the curve plateaus.

**Venous Return**

The venous return curve shows venous return (or RA pressure or CVP) as a function of CO. As CO decreases to zero, the CVP is solely based on compliance of the venous compartment, with the curve shifting to the right for increased blood volume (higher CVP for a given CO) and to the left for decreased blood volume (lower CVP for a given CO) (Figure 5). In contrast to shifting the entire curve, changes in systemic vascular resistance change the slope of the line, decreasing the slope with increased vascular resistance.

**Determinants of Function**

Five main variables exist that determine function, each sensitive to changes in the other variables and so truly interdependent on each other: preload, afterload, heart rate (HR), cardiac rhythm, and contractility.

Preload is the volume of blood in the ventricle at the end of diastole. This is determined by multiple factors including total blood volume, the distribution of that volume, and the contribution of atrial contraction to ventricular filling. As mentioned previously, increased volume load causes increased sarcomere length or stretch, leading to increased sensitivity of the myofibrils to intracellular Ca\(^{2+}\) and resulting in increased tension development of the sarcomere. Thus, the amount of preload on the ventricle determines the amount of stretch of the muscle, promoting increased isometric force developed by the muscle. This plus the increased volume available in the ventricle leads to an increase in the stroke volume (SV) for that cycle.

Afterload is the wall stress on the ventricle during systole, as determined by Laplace’s law, which states that the tension across a thin-walled sphere is directly related to the internal pressure and radius of the sphere: \(T = Pr\). Because the ventricles are not thin-walled spheres, the relationship accounts for average thickness of the ventricular wall. Thus when applied to the intact heart, the equation is expressed as \(T = Pr/t\) where \(T\) represents the tension across the wall.

**Figure 5. Venous return curve**

As cardiac output (CO) decreases to zero, the central venous pressure (CVP) is solely based on compliance of the venous compartment. For any given CO, the curve shifts upward and to the right for increased blood volume (point B to A) (higher CVP for a given CO) and to the left for decreased blood volume (point A to B) (lower CVP for a given CO).
of the ventricle during systole, P represents the transmural pressure across the ventricle at the end of systole, r represents the chamber radius at the end of diastole, and t represents the average thickness of the ventricular wall. Afterload is increased by ventricular dilation (increases r), increased systemic vascular resistance, or increased arterial blood pressure, and it is decreased by ventricular hypertrophy, mechanical ventilation, and positive end-expiratory pressure. Afterload and, thus, wall stress affect SV inversely: For a given preload, SV increases for any decrease in afterload. Prolonged or repeated exposure to increased afterload leads to cardiac hypertrophy as a compensatory response to the chronic increased wall stress, causing increased myocardial oxygen demand to maintain normal SV. Contractility is the ability of the heart to squeeze independent of the other determinants of cardiac function. Both the levels of intracellular Ca\(^{2+}\) available and the responsiveness of the myofibrils affect contractility; an increase in either increases the probability of strong cross-bridge attachments being formed and thus increases the contractility of the myocardium. Contractility can be quantified as the change in pressure over the change in time and can be plotted. Contractility can be quantified by the slope of the line, \(E_s\), created through the end-systolic points on pressure-volume loops generated with varying preloads and afterloads. In the presence of constant preload and afterload, increased contractility will increase SV.

HR can affect CO. Theoretically, if all the other determinants are held constant, CO generally increases directly with increased HR, as indicated in the equation \(CO = HR \times SV\). At the extremes of tachycardia, however, time for diastolic filling is decreased and CO may decrease as well. Increase in HR also increases systolic function by way of the force-frequency relationship, which states that increasing the frequency of stimulation results in an increase in the force of contraction, modulated by Ca\(^{2+}\) availability. Finally, sinus rhythm confers improved CO, as the atrial “kick” in AV synchrony improves ventricular filling and stretch and optimizes ventricular preload prior to ejection. A loss of AV synchrony (junctional rhythms) can result in a 30% decrease in CO.

**Neural Control**

Cardiac function is influenced directly by neuronal innervation. This involves both the sympathetic (adrenergic) and parasympathetic (cholinergic) systems. Sympathetic stimulation (via norepinephrine) results in increasing HR and stroke work (or EF). Conversely, parasympathetic stimulation (via vagal impulses and acetylcholine) causes slowing of HR and decreased atrial contractility without having a significant effect on ventricular contractility. Feedback to the central nervous system (CNS) occurs via various baroreceptors and chemoreceptors. Sympathetic fibers are classified into \(\alpha\) and \(\beta\) subtypes. Stimulation of \(\beta\) receptors causes increased contractility, increased HR, relaxation of the myocardium, and faster impulse conduction through the AV node, ultimately increasing cardiac performance. Although \(\alpha\) receptors are present in the heart, they are present in smaller numbers than \(\beta\) receptors and are more important in the major arteries, where stimulation of the receptors causes vasoconstriction. The \(\alpha\) receptors inhibit central sympathetic outflow and thus decrease blood pressure, protecting from the effects of potentially chronically enhanced catecholamine release in heart failure.

A denervated heart still has sympathetic and parasympathetic receptors as well as intrinsic mechanisms (eg, automaticity of the sinoatrial node results in continued sinus rhythm) and continued response to directly acting catecholamines, thyroid hormone, and angiotensin II. Circulating catecholamines can stimulate the \(\beta\) receptors and augment CO. However, stimulation of baroreceptors and chemoreceptors will not cause tachycardia to the same degree as if the efferent nerves were intact.

Baroreceptors provide a feedback loop to the CNS. The carotid sinus sends feedback via the glossopharyngeal nerve and the aortic arch baroreceptors via the aortic nerve through the vagal nerve; stimulation of either of these by increased arterial pressure signals the CNS to inhibit sympathetic output to the heart and vasculature, resulting in vasodilation and decreased HR and arterial blood pressure. Decreased stretch has the opposite effect, decreasing inhibition of sympathetic stimuli.

**Cardiac Response to Hormonal and Pharmacological Influences**

Both \(\beta_1\) and \(\beta_2\) receptors are present in all chambers of the heart, with \(\beta_1\) present in higher numbers in both the atria and ventricles. Both are coupled to a G\(_{\beta\gamma}\)-protein–adenylyl cyclase pathway, and stimulation increases cyclic adenosine monophosphate, which promotes increased Ca\(^{2+}\) influx through the L-type Ca\(^{2+}\) channels as well as promoting uptake of Ca\(^{2+}\) back into the SR to increase the force of contraction. The \(\beta\) receptors have a higher concentration in the sinoatrial node than the surrounding atrial tissue; thus, stimulation also causes increased HR. So stimulation of \(\beta\) receptors causes increased inotropy and chronotropy. Chronic stimulation by neuronal norepinephrine or circulating epinephrine, as is the case in chronic heart failure, causes down-regulation of \(\beta\) receptors and makes the heart less responsive to their effects. In addition to its negative inotropic and chronotropic effects, \(\beta\)-blockade causes up-regulation of those receptors, allowing the catecholamines to be more effective.
The α receptors are found in the myocardium but to a much lesser degree than their β counterparts. The net result is that α-adrenergic effects are the primary modulator of vascular tone. Stimulation of both α₁ and α₂ receptors in the vasculature causes vasoconstriction at the arteriolar and venular level. The α₁ receptors are present in the myocardium, and stimulation causes modest positive inotropic effects. As well, α₂ receptors can be found presynaptically, where stimulation inhibits release of the neurotransmitter, resulting in a centrally mediated vasodilation. In normal, conscious individuals, these central hypotensive effects predominate over the peripheral vasoconstrictive effects. An α-blockade has the opposite effect, in that α₁-blockade allows vasodilation and α₂-blockade allows for increased presynaptic release of norepinephrine in addition to its direct vasodilation activity. Cardiac responses to specific hormonal and pharmacological agents can be found in Table 3.

### Developmental Changes

Compared with an adult, the neonatal myocyte has fewer myofibrils overall and fewer per cross-sectional area. These myofilaments are relatively disorganized at birth, with no defined orientation; as the cells mature, the myofilaments become decidedly more organized, aligning parallel to the long axis of the myocyte. The longer myocytes have more capacity to shorten via the Frank-Starling mechanism, leading mature hearts to have increased contractility compared with neonatal hearts. In addition, actin isoforms change within the cells during the first year of life, increasing contractility. Myocardial stiffness is increased at birth relative to the mature heart. As the ventricles mature, they become more compliant, allowing for increased filling. Neonatal CO overcomes the decreased compliance and SV limitation by increasing HR. Neonatal CO is SV limited and highly dependent on HR.

### Table 3. Cardiac Response to Hormonal and Pharmacologic Influences

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Excitation-contraction coupling process.</td>
<td>Augments myocardial contractility and thus improves cardiac output.</td>
</tr>
<tr>
<td>Cardiac glycoside (digoxin)</td>
<td>Increases contractility by augmenting cytosolic Ca²⁺ via inhibition of sodium-potassium-adenosine triphosphatase (Na⁺K⁺ATPase).</td>
<td>Net result of increased cytosolic Ca²⁺. This alters excitation-contraction coupling and results in increased contractility and increased vagal tone, resulting in slower heart rate and decreased conduction through the atrioventricular node.</td>
</tr>
<tr>
<td>Bipyridines (milrinone)</td>
<td>Inhibit phosphodiesterase 3, resulting in reduced hydrolysis of cyclic adenosine monophosphate and increases in L-type Ca²⁺ channels that open. These events increase the amount of Ca²⁺ during each action potential, causing more Ca²⁺ to be released by the stroke volume. The stroke volume increases the speed of uptake of Ca²⁺ after contraction has occurred.</td>
<td>Positive inotropy, positive lusitropy, and afterload reduction due to arterial and venous vasodilatation.</td>
</tr>
<tr>
<td>Natriuretic peptides (ANP, BNP)</td>
<td>Reduce preload by stimulating natriuresis and diuresis in the kidneys and reduce afterload by vasodilation.</td>
<td>Increase cardiac output without affecting contractility.</td>
</tr>
<tr>
<td>Nitrates (sodium nitroprusside)</td>
<td>Nitric oxide acts on vascular smooth muscle to increase cyclic guanosine monophosphate, resulting in decreased intracellular Ca²⁺ concentrations.</td>
<td>Afterload reduction via vasodilation.</td>
</tr>
</tbody>
</table>
In mature myocytes, calcium-induced calcium release is the major source of increased cytosolic Ca\(^{2+}\). In the immature heart, however, despite its having adequate Ca\(^{2+}\) stores present in the SR, stimulation of ryanodine receptors does not result in significant change in cytosolic Ca\(^{2+}\), either due to immaturity of the ryanodine receptors themselves or due to lack of a fully formed T-tubule network. Overall, this makes neonates much more dependent on plasma levels of Ca\(^{2+}\) for maintenance of cardiac function.

Although sympathetic innervation is not fully developed at birth, the myocardial cells still express adrenergic receptors and are susceptible to stimulation by circulating catecholamines. In fact, the relatively increased inotropic state seen as the heart transitions from fetus to neonate is likely due to increased β-receptor stimulation, resulting in a constantly high contractile state. Neonates are far more sensitive to β\(_2\)-receptor agonists than are their mature counterparts. Without direct neuronal stimulation, neonatal hearts are dependent on circulating catecholamine stimulation.

The time frame in which a particular cardiac lesion presents depends on both the normal changes in cardiac structure that occur with development and the pathophysiological effects of that particular lesion. D-transposition of the great arteries consists of 2 parallel circulations instead of the usual series circulation; thus, transition from fetal to extrauterine life causes severe cyanosis, and these infants present within the first 24 to 48 hours of life. Critical obstructive lesions of the right side of the heart (including pulmonary atresia, tetralogy of Fallot with pulmonary atresia, critical pulmonary stenosis, tricuspid atresia, and severe Ebstein anomaly) are also likely to present during this time, with cyanosis that worsens as the ductus closes. Critical obstructive lesions of the left side of the heart, including hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and obstructive total anomalous pulmonary venous return, may present at this time with evidence of poor perfusion and outright shock that also worsens as the ductus closes. In general, ductal dependent lesions present within the first week of life.

Lesions that do not cause left- or right-sided obstruction but instead result in significant pulmonary overcirculation due to left-to-right shunting at the ventricular level (unrestrictive VSD, AVSD) may not present until 4 to 6 weeks of life. This coincides with the decrease in pulmonary vascular resistance to normal adult levels. Low-velocity shunting occurs, resulting in volume overload with signs of pulmonary overcirculation. In contrast, the murmur of a small and restrictive VSD may present within the first few days of life, as the pulmonary vascular resistance drops to below systemic levels shortly after birth. A large ASD may be detected within the first few years of life due to a wide split S2 or a systolic ejection murmur heard due to the volume load on the right side of the heart resulting in relative pulmonary stenosis.

### Mechanical Dysfunction

Heart failure is a complex pathophysiological syndrome involving many different factors that may include either systolic or diastolic dysfunction. A complete review of heart failure can be found in Chapter 8.

### Systolic Dysfunction

Evaluation for systolic dysfunction includes noninvasive imaging (primarily echocardiography) and laboratory testing for neurohumoral activation. Two-dimensional echocardiography can be used to evaluate for ejection fraction (EF) and fractional shortening, which are slightly different ways to quantify function. The EF is calculated by indexing the difference between EDV and end-systolic volume (ESV), which is equal to SV for that beat, as a percentage of the EDV, or EF = (EDV – ESV)/EDV × 100. Fractional shortening is calculated in the same format but instead uses the end-diastolic and systolic diameter as measured in the parasternal long-axis view. Other echocardiographic parameters of function include the maximal rate of pressure increase during ventricular contraction (peak dP/dt), tissue Doppler, and Doppler myocardial performance index.

Neurohumoral activation levels can be used to gauge the level of systolic dysfunction. Extensive data exist in adults correlating the levels of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) to severity of heart failure. Attention has been paid in the past few years to validate the utility of these measurements in children. Levels of NT-proBNP have been shown to correlate well with echocardiographic indexes of LV dysfunction.

The causes of systolic dysfunction are varied and multifactorial but can be broken down into a few generalized categories. The most common cause of cardiac dysfunction in the United States is secondary to congenital heart disease. In children with normally formed hearts, cardiomyopathies are the most common cause. Cardio-pulmonary bypass–induced myocardial dysfunction is the most common cause of acute myocardial dysfunction in pediatrics, occurring generally 6 to 12 hours after separation from bypass.
The mechanisms underlying myocardial dysfunction can involve disruption at any level of the contraction process, such as alterations in calcium signaling, changes in the proteins in the contractile apparatus, and disruption of the transmission of the contraction to the extracellular matrix. Influx of Ca\(^{2+}\) through L-type Ca\(^{2+}\) channels is decreased due to the decreased number of functionally active channels, leading to a prolonged and attenuated action potential. Less Ca\(^{2+}\) entering the cell means less calcium-induced calcium release from the SR. Ca\(^{2+}\) stores in the SR themselves are decreased. The overall force-frequency response is impaired. All of this leads to decreased contractility at the individual sarcomere. Decreased clearance of the intracytosolic Ca\(^{2+}\) results in elevated intracellular levels and impaired relaxation.

Disruptions in the dystrophin protein complex lead to systolic dysfunction. In order for the contraction that occurs at the sarcomere level to transmit across the sarcolemma into the extracellular matrix beyond the individual myocyte, dystrophin must connect the actin filaments to that extracellular matrix, with portions of the complex embedded in the sarcolemma itself. Disruption at any point throughout the complex, as is seen with the muscular dystrophies, results in decreased myocardial function.

**Diastolic Dysfunction**

Diastole is composed of 2 general parameters: active relaxation and passive stiffness, beginning with the release of Ca\(^{2+}\) from TnC. This “recycling” of Ca\(^{2+}\) requires energy and results in isovolumic relaxation. Isovolumic relaxation time generally lengthens when the relaxation process is disrupted and isovolumic pressure decline is slow.

Mitrail inflow patterns have been used to evaluate LV diastolic function. Doppler echocardiography of early diastolic filling yields the mitral E wave, the deceleration rate of which is a measure of LV compliance (faster deceleration indicates increased stiffness). The E-wave peak velocity is increased in the presence of impaired relaxation. In late diastole, atrial contraction produces another wave on Doppler, the mitral A wave, typically occurring after active relaxation is complete and thus reflecting only LV compliance. The ratio of E and A waves is normally greater than 1 (E > A). Early in diastolic dysfunction, the E wave is diminished and this relationship can become reversed, but as failure progresses, increased LA pressures and decreased LV compliance can cause pseudo-normalization of this relationship.

Isovolumic relaxation time can be measured on M-mode echocardiography by measuring the time interval from the closing of the aortic valve to the opening of the mitral valve. It can also be measured by Doppler, by determining the time interval from the end of aortic flow to the start of flow into the LV across the mitral valve.

Postoperatively, intracardiac or centrally placed catheters can be used to directly measure CVP and enable continuous estimation of RV diastolic pressures. These pressures are particularly important in tetralogy of Fallot (and other lesions that cause significant RV hypertrophy) as patients frequently exhibit restrictive RV physiology, where the RV functions as more of a passive conduit for antegrade blood flow during atrial systole. This abnormal RV diastolic dysfunction causes increased filling pressures and diminished CO that can contribute significantly to the low CO state seen after cardiopulmonary bypass. Similarly, chronic left-sided obstruction and resulting hypertrophy have been shown to cause persistent diastolic dysfunction, even after the obstruction is relieved.

Hypertrophic cardiomyopathy causes significant derangements in diastolic function. Increased myocardial mass and abnormal collagen deposition cause derangements in myocardial relaxation, resulting in stiffening of the LV. A number of disease processes secondarily cause derangements in diastolic function, including Fabry disease, Pompe disease, and other storage diseases that cause infiltrative forms of LV hypertrophy. Noonan syndrome cardiomyopathy may resemble hypertrophic cardiomyopathy, with the same effects on diastolic function. Other entities include mitochondrial myopathies (like Kearns–Sayre syndrome), metabolic myopathies (fatty acid oxidation defects), and other infiltrative myopathies (glycogen storage diseases, Hunter disease, Hurler disease).

Isolated diastolic dysfunction is the hallmark of restrictive cardiomyopathy. Left ventricular function and wall thickness are normal, but relaxation is impaired, leading to dilated atria and high filling pressures. Causes include exposure to radiation and anthracyclines as well as less frequent factors like Gaucher and Hurler disease, indicating a failure in passive stiffness due to derangements in the extracellular matrix (eg, fibrosis, inflammation). However, the cause of most cases of restrictive cardiomyopathy in children remains unknown. Constrictive pericarditis can mimic the phenotype (without the atrial dilation), but the underlying myocardium is normal.
SUGGESTED READINGS


