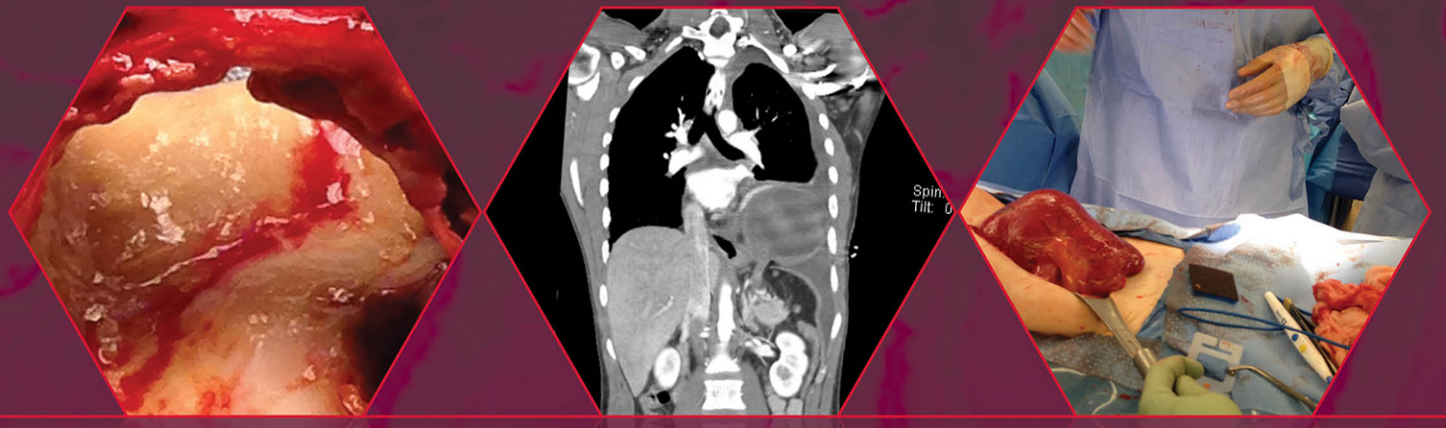
THIRD EDITION

FIRST AID FOR THE® BASIC SCIENCES

Organ Systems



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DEDICATION

To the contributors to this and future editions, who took time to share their knowledge, insight, and humor for the benefit of students and physicians everywhere.

and

To our families, friends, and loved ones, who supported us in the task of writing this book.

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Preface

With this third edition of *First Aid for the Basic Sciences: Organ Systems*, we continue our commitment to providing students with the most useful and up-to-date preparation guides for the USMLE Step 1. For the past year, a team of authors and editors have worked to update and further improve this third edition. This edition represents a major revision in many ways.

- Every page has been carefully reviewed and updated to reflect the most high-yield material for the Step 1 exam.
- New high-yield figures, tables, and mnemonics have been incorporated.
- Margin elements, including flashcards, have been added to assist in optimizing the studying process.
- Hundreds of user comments and suggestions have been incorporated.
- Emphasis is on deeper understanding and integration of critical concepts.

This book would not have been possible without the help of the hundreds of students and faculty members who contributed their feedback and suggestions. We invite students and faculty to please share their thoughts and ideas to help us improve *First Aid for the Basic Sciences: Organ Systems*. (See How to Contribute, p. xiii.)

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Boston William Hwang

How to Use This Book

Both this text and its companion, *First Aid for the Basic Sciences: General Principles*, are designed to fill the need for a high-quality, in-depth, conceptually driven study guide for the USMLE Step 1. They can be used either alone or in conjunction with the original *First Aid for the USMLE Step 1*. In this way, students can tailor their own studying experience, calling on either series, according to their mastery of each subject.

Medical students who have used the previous editions of this guide have given us feedback on how best to make use of the book.

- **It is recommended that you begin using this book as early as possible** when learning the basic medical sciences. We advise that you use this book as a companion to your preclinical medical school courses to provide a guide for the concepts that are most important for the USMLE Step 1.
- As you study each discipline, **use the corresponding section in *First Aid for the Basic Sciences: Organ Systems*** to consolidate the material, deepen your understanding, or clarify concepts.
- As you approach the test, use both *First Aid for the Basic Sciences: General Principles* and *First Aid for the Basic Sciences: Organ Systems* to review challenging concepts.
- Use the margin elements (ie, Flash Forward, Flash Back, Key Fact, Clinical Correlation, Mnemonic, Flash Cards) to test yourself throughout your studies.

To **broaden** your learning strategy, you can **integrate** your *First Aid for the Basic Sciences: Organ Systems* study with *First Aid for the USMLE Step 1*, *First Aid Cases for the USMLE Step 1*, and *First Aid Q&A for the USMLE Step 1* on a chapter-by-chapter basis.

Acknowledgments

This has been a collaborative project from the start. We gratefully acknowledge the thoughtful comments and advice of the residents, international medical graduates, medical students, and faculty who have supported the editors and authors in the development of *First Aid for the Basic Sciences: Organ Systems*.

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Furthermore, we wish to give credit to our amazing editors and authors, who worked tirelessly on the manuscript. We never cease to be amazed by their dedication, thoughtfulness, and creativity.

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How to Contribute

To continue to produce a high-yield review source for the USMLE Step 1, you are invited to submit any suggestions or corrections. We also offer paid internships in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for:

- New facts, mnemonics, diagrams, and illustrations
- High-yield topics that may reappear on future Step 1 examinations
- Corrections and other suggestions

For each new entry incorporated into the next edition, you will receive up to a **$20 Amazon.com gift card** as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, or ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the *AMA Manual of Style* recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc).

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: **www.firstaidteam.com.**

Alternatively, you can email us at: **firstaidteam@yahoo.com.**

NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

AUTHOR OPPORTUNITIES

The *First Aid* author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series.

English writing/editing experience, familiarity with Microsoft Word, and Internet access are required. For more information, email us at **firstaidteam@yahoo.com** with a résumé and summary of your interest or sample work.

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CHAPTER 1

Cardiovascular

Embryology

DEVELOPMENT OF THE HEART

Embryonic Heart Structures and Adult Derivatives

By the third week of development, the rapidly growing embryo can no longer rely on simple diffusion from the placenta for its metabolic and oxygen requirements. It is no surprise, then, that the heart is the first functioning organ in vertebrate embryos, and a primitive heart begins to beat by week 4 of development (Table 1-1).

Development and Looping of Heart Tube

A primitive heart tube develops from mesodermal cells at the cranial end of the embryo during gastrulation. The steps of looping are as follows:

1. Primitive heart chambers lined with endothelial cells form along the cranial-caudal axis of the heart tube.
2. Rapid elongation of the heart tube occurs in a confined space (the pericardial cavity), requiring that it bend into a U-shaped loop that places the primitive atrium behind the more-prominent primitive ventricle. Note that in the early stages, the primitive atrium is connected to the ventricle via a common **atrioventricular (AV) canal.**

CLINICAL CORRELATION

Defects in **dynein** (protein in cilia involved in L/R asymmetry) or cardiac looping can lead to **dextrocardia,** a condition in which the heart lies on the right side of the thorax. It often accompanies Kartagener syndrome, an autosomal recessive genetic disorder that results in dysfunctional cilia in the reproductive and genitourinary tracts as well.

Formation of Septa

Heart septa divide the atrioventricular canal, atrium, ventricle, and aortiocopulmonary (ventricular outflow) tract into discrete chambers. Septa form between the fourth and sixth weeks of development from inward growth of the innermost (endocardial) cardiac surface. Although all septation events occur simultaneously, for clarity, these steps are detailed individually for each structure below.

CLINICAL CORRELATION

Patent foramen ovale (PFO) results from failure of the septum primum and septum secundum to fuse after birth. Because no atrial septal tissue is absent, it is not a true atrial septal defect (ASD). It is usually asymptomatic if left atrial pressure exceeds right atrial pressure, which forces the septum primum—although not fused—to stay closed up against the septum secundum.

Atrioventricular Canal Septum

The common AV canal is split into two canals by **endocardial cushions,** which are endocardial inward growths that fuse together from the anterior and posterior canal walls.

TABLE 1-1. Embryonic Heart Structures and Adult Derivatives

EMBRYONIC STRUCTURE	ADULT STRUCTURE
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Primitive ventricle	Trabeculated parts of left and right ventricles
Primitive atrium	Trabeculated parts of left and right atria
Left horn of sinus venosus (SV)	Coronary sinus (largest venous drainage of heart)
Right horn of SV	Smooth part of right atrium
Right common cardinal vein and right anterior cardinal vein	Superior vena cava
Vitelline veins	Portal system

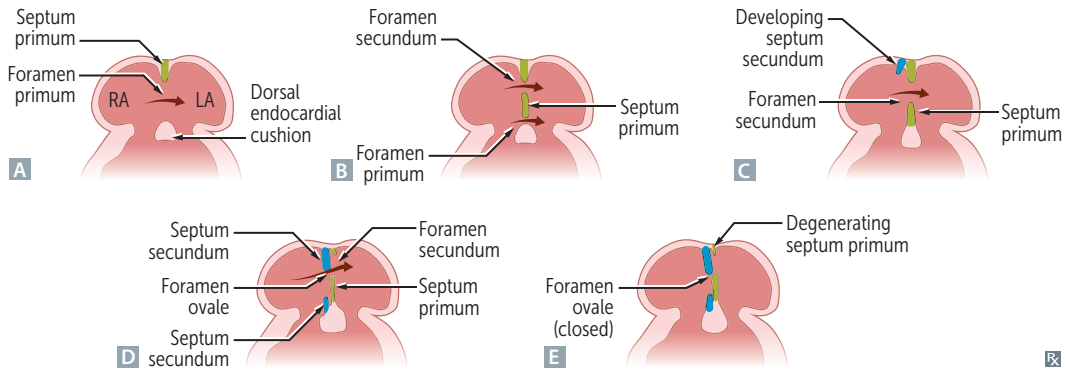


FIGURE 1-1. Embryologic development of the atrial septum.

Abnormal fusion of endocardial cushions can lead to **endocardial cushion defects,** which are a broad class of congenital heart defects with abnormal septation of the atria, ventricle, and/or AV canal.

Atrial Septum

The atrial septum is responsible for the initial division of the primitive atrium into the left and right atria. The steps of development are as follows:

1. The **septum primum** begins to grow toward the atrioventricular (AV) cushions (Figure 1-1A). The orifice (ie, ostium) between the leading edge of the septum primum and the AV cushions is termed the **ostium primum** (aka foramen primum). The ostium primum is obliterated when the septum primum reaches the AV septum.
2. The **ostium secundum** (aka foramen secundum) is formed as tissue degenerates in the superior septum primum (Figure 1-1B).
3. The **septum secundum** forms alongside the right edge of the septum primum (Figure 1-1C).
4. The septum secundum contains the **foramen ovale,** which allows blood to be shunted from the right atrium (RA) to the left atrium (LA) during fetal life (Figure 1-1D). The septum primum to the left of the septum secundum helps act as a one-way valve for right-to-left flow. After birth, the increase in pressure in the LA causes the septum primum to close and fuse against the septum secundum, forming the mature interatrial septum (Figure 1-1E).

An **atrial septal defect (ASD)** is an opening in the atrial septum, allowing blood to flow between the atria (Figure 1-2). The **most common form is the ostium secundum type** located in the region of the foramen ovale, which is due to excessive resorption of the septum primum or inadequate formation of the septum secundum. Patients are typically asymptomatic until adulthood, but the clinical course depends on the size of the defect.

Classic signs of ASD include the following:

- **Wide, fixed splitting of S_2:** Normal splitting occurs because of increased right ventricle preload during inspiration that delays closure of pulmonary valve. In ASD, the right ventricle is always preload overloaded from the left-to-right shunt, and thus there is no increase in splitting during inspiration.
- **Pulmonic flow murmur** due to increased flow across the pulmonary valve heard best in the second intercostal space along the left sternal border.

Interventricular Septum

The interventricular septum consists of two parts: the **muscular** portion and the **membranous** portion.

CLINICAL CORRELATION

Due to left-to-right shunting in ASD, right atrial and ventricle enlargement occurs. On ECG, this results in tall P waves (best seen in leads II and V_1/V_2), which reflect atrial enlargement, and signs of RVH (eg, QRS right axis deviation).

CLINICAL CORRELATION

A failure of the septum primum to fuse with the endocardial cushions can lead to an **ostium primum** ASD at the inferior part of the atrial septum. This type of endocardial cushion defect is associated with trisomy 21.

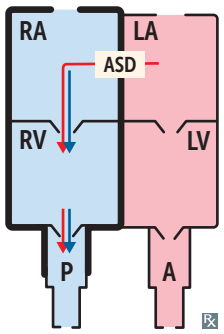


FIGURE 1-2. Atrial septal defect (ASD). In ASD, there is a left-to-right shunt between the atria. The right atrium (RA), right ventricle (RV), and pulmonary artery (P) become enlarged (indicated by bolded borders of heart chambers) owing to the influx of additional blood via the ASD left-to-right shunt. A, aorta; LA, left atrium; LV, left ventricle.

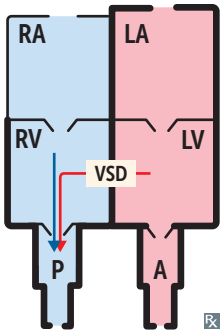


FIGURE 1-3. Ventricular septal defect (VSD). In VSD, there is a left-to-right shunt between the ventricles. The left atrium (LA) and left ventricle (LV) become enlarged (indicated by bolded borders of heart chambers) as a result of blood flow through this left-to-right shunt into the pulmonary artery and back into the left atrium and ventricle. Right ventricle (RV) and right atrium (RA) enlargement may also be present. Over time, Eisenmenger syndrome can occur as a result of the VSD. A, aorta; P, pulmonary artery.

MNEMONIC

The 5 T's of early cyanosis (right-to-left shunts):

1. **T**runcus arteriosus (1 vessel)
2. **T**ransposition (2 switched vessels)
3. **T**ricuspid atresia (3 = tri)
4. **T**etralogy of Fallot (4 = tetra)
5. **T**APVR (5 letters in the name)

CLINICAL CORRELATION

Persistent truncus arteriosis is often associated with **DiGeorge syndrome.**

MNEMONIC

***Tetralogy of Fallot*—PROVe**

Pulmonic stenosis
RV hypertrophy
Overriding aorta
VSD

- The **muscular** interventricular **septum** forms as an upward expansion of the base of the primitive ventricle. It extends toward the AV septum but does not reach it; the resulting gap is the **interventricular foramen.**
- The **membranous** interventricular **septum** is created by the fusion of the aorticopulmonary septum with the muscular intraventricular septum. It grows downward from the AV cushions and fuses with the muscular interventricular septum, obliterating the interventricular foramen.

Ventricular septal defect (VSD), an abnormal opening in the interventricular septum, is **the most common congenital heart malformation** (Figure 1-3). The most common location is in the membranous interventricular septum, resulting from incomplete fusion of the AV cushions with aorticopulmonary septum. Clinical manifestations of a VSD vary depending on the size of the defect. Fifty percent of small VSDs undergo complete or sufficient partial closure by age 2 and do not require intervention. Larger VSDs result in left-to-right shunting of blood, and, as a result, may present with late cyanosis.

- A classic symptom is **easy fatigability.**
- Cardiac auscultation reveals a **harsh holosystolic murmur** heard best at the left lower sternal border.

Aorticopulmonary Septum

The **aorticopulmonary (AP) septum** is derived from **neural crest cells** that migrate into the primitive ventricular outflow tract. It is responsible for separating the **truncus arteriosus** into the aorta and pulmonary artery. As the septum descends, it **spirals 180 degrees** so that the aorta becomes the left ventricular outflow tract and the pulmonary trunk becomes the right ventricular outflow tract. Failure of spiraling leads to congenital malformations that involve **right-to-left shunting and early cyanosis in the newborn period.**

- **Persistent truncus arteriosus** results from abnormal migration of neural crest cells and subsequent **failure of formation of the AP septum.** Therefore, separation of the left ventricular and right ventricular outflow tracts never occurs. The aorta and pulmonary trunk form a common tract leaving the ventricles, which allows mixing of oxygenated and deoxygenated blood.
- **Transposition of the great vessels** occurs when **the AP septum fails to spiral 180 degrees.** The left ventricle (LV) is connected to the pulmonary trunk, and the right ventricle (RV) is connected to the aorta (Figure 1-4). This condition results in a complete **right-to-left shunt** and **early cyanosis.**
- **Tetralogy of Fallot** is caused by **anterior displacement of the AP septum.** The four abnormalities are overriding aorta, pulmonic stenosis, RV hypertrophy, and VSD (Figure 1-5). The primary defect is termed an "**overriding aorta,**" because the misplaced aorta partially obstructs the right ventricular outflow tract, leading to **right ventricular outflow obstruction (pulmonic stenosis).** Pulmonic stenosis leads to increased pressures in the RV and subsequent **right ventricular hypertrophy.** The **membranous VSD** results from a failure of fusion between the AP septum and the muscular portion of the intraventricular septum (IVS). **Right-to-left shunting** results in **early cyanosis.**

SUMMARY OF CONGENITAL HEART LESIONS

Congenital heart lesions are classified as **cyanotic** or **noncyanotic** based on the appearance of the infant at birth. **Cyanosis** is the purple-blue skin and mucous membrane discoloration due to an increased level of deoxyhemoglobin from decreased oxygen levels in systemic circulation.

Cyanotic Congenital Heart Lesions

Cyanosis is caused by lesions that lead to **right-to-left shunting** of blood, in which blood coming from the right ventricle bypasses lungs to various degrees before entering systemic circulation.

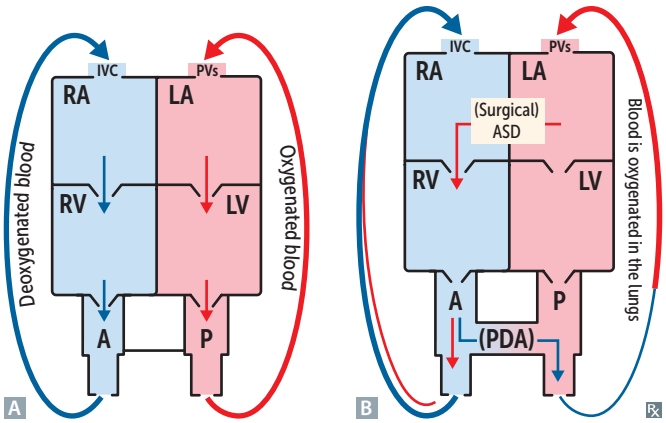


FIGURE 1-4. Transposition of the great vessels. Developmental defect in which the left ventricle connects to the pulmonary artery and the right ventricle connects to the aorta, resulting in two closed circuits. A Without a patent ductus arteriosus (PDA) and atrial septal defect (ASD), a closed circuit results that is incompatible with life. B With a PDA and ASD, a left-to-right shunt is created at the atrial level, and systemic circulation can receive oxygenated blood. Note: For infants awaiting more definitive surgical repair, prostaglandin E_1 (PGE) can be administered to maintain a PDA and an ASD can be surgically created. A, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; P, pulmonary artery; PVs, pulmonary veins; RA, right atrium; RV, right ventricle.

These lesions can be remembered as the 5 Ts:

1. **T**etralogy of Fallot (most common cause of early cyanosis)
2. **T**ransposition of the great vessels
3. **T**runcus arteriosus
4. **T**otal anomalous pulmonary venous return
5. **T**ricuspid atresia (Figure 1-6)

Squatting increases left-sided pressure or systemic vascular resistance (SVR) by compression of femoral arteries; this can make SVR higher than PVR (pulmonary vascular resistance, or right-sided pressure) and thus may decrease right-to-left shunting and allow more blood to pass through the pulmonary circulation before entering the systemic circulation, alleviating symptoms of cyanosis.

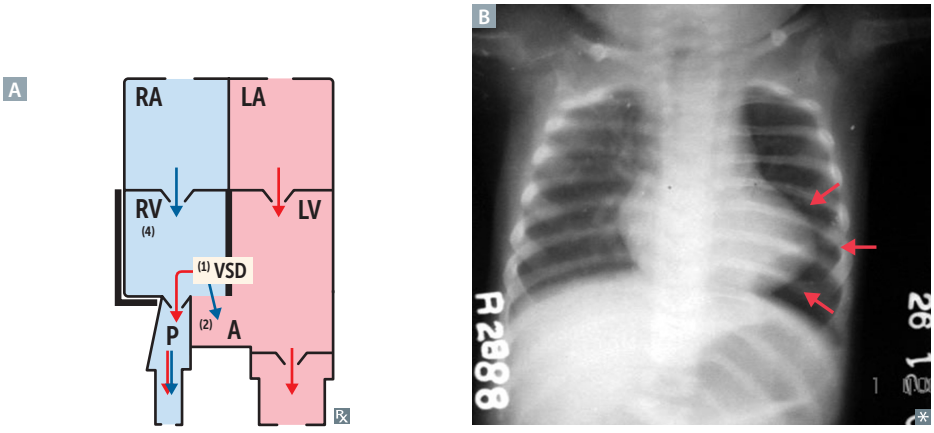


FIGURE 1-5. Tetralogy of Fallot. A Four concurrent defects: (1) Ventricular septal defect (VSD), (2) an overriding aorta, causing (3) right ventricular outflow obstruction (pulmonic stenosis) and subsequent (4) right ventricular hypertrophy. The extent of R-L shunting is determined by the degree of pulmonic stenosis present. B As seen on x-ray, the heart appears boot-shaped (arrows). (A, aorta; LA, left atrium; LV, left ventricle; P, pulmonary artery; RA, right atrium; RV, right ventricle.)

KEY FACT

Deoxyhemoglobin levels must be at least 4 g/dL, which correlates to an oxygen saturation of 80–85%, before clinically apparent cyanosis can be detected. Anemia by itself never causes cyanosis.

CLINICAL CORRELATION

Although bicuspid aortic valves often calcify prematurely in adults, leading to eventual aortic stenosis, it is also the most common cause of isolated aortic regurgitation in young adults in developed countries.

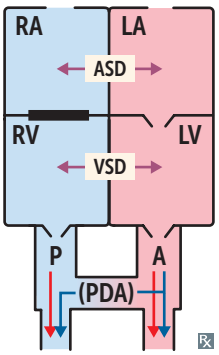


FIGURE 1-6. Tricuspid atresia. Failure of the tricuspid valve to develop, preventing blood from flowing from the right atrium (RA) into the right ventricle (RV). In order for oxygenated blood to reach the body, an atrial septal defect (ASD) and ventricular septal defect (VSD) must simultaneously be present in order for blood from the RA to reach the RV and flow to the lungs to be oxygenated. A patent ductus arteriosus (PDA) can be maintained via the administration of prostaglandin E_2 (PGE_2) to permit blood flow from an ASD into the pulmonary artery (P), thereby allowing blood from the RA to flow into the P for oxygenation.

Acyanotic Congenital Heart Lesions

Defects that do not produce early cyanosis at birth are termed **acyanotic** lesions and can be due to **stenotic lesions** or **left-to-right shunts.**

Stenotic Lesions

Coarctation of the Aorta

Coarctation of the aorta is aortic narrowing that typically occurs proximal to the ductus arteriosus (can be termed "preductal" or "postductal" based on location of the stenosis in relation to the ductus arteriosus), resulting in increased LV afterload. Coarctation can be symptomatic early (infantile form) or later in life (adult form), depending on severity of stenosis and if there is a patent ductus arteriosus (PDA) at birth:

- **Infantile form:** Aortic narrowing proximal to a PDA, which can lead to cyanosis of the lower half of the body due to right-to-left shunting via the PDA to vessels below the aortic arch. Note that the upper half of the body is supplied by branches of the aortic arch, which are unaffected by the distal right-to-left shunt (Figure 1-7A).
- **Adult form:** Aortic narrowing distal to the aortic arch without PDA (Figure 1-7B). Presents later in life, with hypertension in upper extremities (supplied by the branches of the aortic arch) and hypotension in lower extremities from decreased blood flow across the coarctation and absence of PDA. As a result, collateral circulation usually develops to route blood from the aorta to the lower extremities (from the proximal aorta via the subclavian artery, to the internal thoracic artery, to the superior epigastric artery, to the inferior epigastric artery, to the external iliac artery). Increased blood flow to the intercostal arteries causes them to dilate and eventually erode into ribs. This process results in the characteristic "rib notching" associated with coarctation of the aorta.

Congenital Aortic Stenosis

Congenital aortic stenosis is caused most often by abnormal development of the aortic valve that results in stenosis in the neonate. Bicuspid valves generally do not cause any obstruction at birth, but are more susceptible to calcification and fibrosis than normal tricuspid valves and often result in early-adulthood aortic stenosis.

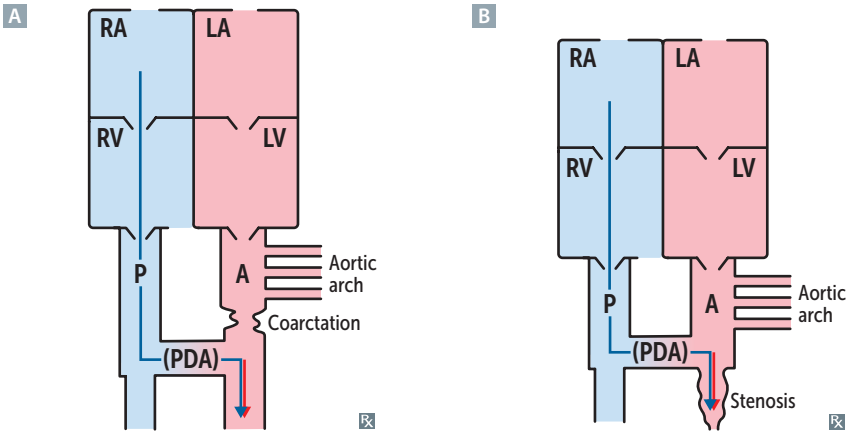


FIGURE 1-7. Preductal (infantile) and postductal (infantile) aortic coarctation. A Narrowing of the aorta proximal to the ductus arteriosus. This leads to decreased blood flow distal to the coarctation, and a right-to-left shunt if the patent ductus arteriosus (PDA) is kept open (can lead to cyanosis of the lower half of the body). B Narrowing of the aorta distal to the ductus arteriosus. This leads to decreased blood flow to the lower body. A, aorta; LA, left atrium; LV, left ventricle; P, pulmonary artery; RA, right atrium; RV, right ventricle.

FLASH FORWARD

Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is used to close a patent ductus arteriosus (PDA). Exogenous administration of prostaglandins (PGE_2) is used to keep a PDA open.

Left-to-Right Shunts

Ventricular Septal Defect

VSD is one of the most common congenital cardiac abnormalities; see earlier VSD discussion.

Atrial Septal Defect

An atrial septal defect has a loud S_1 and a wide, fixed split S_2; see earlier ASD discussion.

Patent Ductus Arteriosus

Within hours after birth, the increased oxygenation of blood and decreased circulation of prostaglandins through the ductus arteriosus mediate closure of the ductus. When this does not occur, a **patent ductus arteriosus** (PDA) can persist, leaving a connection between the left pulmonary artery and aortic arch (Figure 1-8). Because the left heart has higher pressures than right heart at birth, a left-to-right shunt develops, with blood flowing from the aorta into the pulmonary artery. It is most common in premature infants who are hypoxic. It does not result in early cyanosis, because there is no right-to-left shunting.

- Results in a continuous "machine-like" murmur because blood is flowing throughout systole and diastole from aorta into pulmonary artery.
- Administration of prostaglandin inhibitors (eg, indomethacin, nonsteroidal anti-inflammatory drugs [NSAIDs]) enhances closure of the PDA.

If these left-to-right shunts do not close, and high blood flow continues through the pulmonary circulation, the pulmonary arterial system becomes hypertrophic and even fibrotic, resulting in pulmonary hypertension. Increased right-sided pressure leads to right ventricular hypertrophy. When the right-sided pressure becomes higher than left-sided pressure, the shunt reverses and becomes right-to-left. This shunt reversal is termed **Eisenmenger syndrome** and causes **late cyanosis** in early adulthood from shunting of deoxygenated blood into systemic circulation.

CONGENITAL CARDIAC DEFECT ASSOCIATIONS

Certain disorders are associated with particular congenital cardiac malformations (Table 1-2).

TABLE 1-2. Disorders and Associated Cardiac Defects

DISORDER	CARDIAC DEFECT
22q11 Deletions	Truncus arteriosus, tetralogy of Fallot
Down syndrome	VSD, ASD, AV septal defect (endocardial cushion defect)
Turner syndrome	Coarctation of the aorta, bicuspid aortic valve, aortic dissection in adulthood
Offspring of a diabetic mother	Most commonly, transposition of the great vessels, VSD, and aortic stenosis
Congenital rubella	Septal defects, PDA, pulmonary artery stenosis
Marfan syndrome	Aortic insufficiency (due to aortic root dilation), mitral valve prolapse, aortic aneurysm/dissection

ASD, atrial septal defect; AV, atrioventricular; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

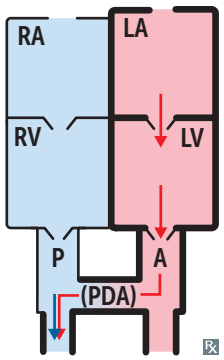


FIGURE 1-8. Patent ductus arteriosus (PDA). In PDA, a left-to-right shunt is present between the aorta (A) and pulmonary artery (P) due to the persistence of prostaglandins, a decrease of which normally triggers the closure of the PDA shortly after birth. A persistent PDA results in a continuous, machine-like murmur throughout systole and diastole. The left atrium (LA), left ventricle (LV), P and A become enlarged as a result of increased blood return to the left side of the heart. RA, right atrium; RV, right ventricle.

KEY FACT

Enlargement of the LA, a characteristic finding in mitral valve (MV) insufficiency, may cause dysphagia due to impingement on the esophagus.

CLINICAL CORRELATION

The use of certain drugs during pregnancy (lithium, benzodiazepines) has been associated with a rare congenital defect called Ebstein anomaly, in which tricuspid valve leaflets are located deep in the right ventricle. If there is an associated ASD, build-up of blood in the right atrium secondary to poor tricuspid valve function can lead to right-to-left shunting and cyanosis.

QUESTION

A 30-year-old magician swallows an open safety pin as part of his show. Which chamber of the heart is most likely to be punctured?

CLINICAL CORRELATION

Small "paraumbilical" veins remain in the ligament teres, and in severe portal hypertension often associated with cirrhosis, shunting of blood can occur through this portacaval anastomosis from the hepatic portal circulation to veins of the anterior abdominal wall to reduce portal pressure. This results in a "caput medusae" sign, which describes the snakelike appearance of engorged anterior abdominal veins.

MNEMONIC

Young **L**iver **S**ynthesizes **B**lood.

MNEMONIC

From fetal to adult hemoglobin:
Alpha **A**lways, **G**amma **G**oes, **B**ecomes **B**eta.

FLASH FORWARD

Because the switch from fetal (alpha and gamma chains) to adult hemoglobin (alpha and beta chains) takes several months to reach a new steady-state after birth, it explains why β-thalessemias (inherited blood disorders with decreased or no synthesis of the beta chains of hemoglobin) usually manifest later in infancy, around 6 months of age.

MNEMONIC

Prostaglandins **E**1 and **E**2 k**EE**p PDA open.

ANSWER

Left atrium, owing to its proximity to the esophagus.

FETAL-POSTNATAL DERIVATIVES

Some important fetal structures and their postnatal counterparts follow:

- Alla**N**tois → urachus—**mediaN** umbilical ligament (Note: urachus is part of allantoic duct between bladder and umbilicus.)
- Ductus arteriosus → ligamentum arteriosum
- Ductus venosus → ligamentum venosum
- Foramen ovale → fossa ovalis
- Notochord → nucleus pulposus
- Umbi**L**ical arteries → **mediaL** umbilical ligaments
- Umbilical vein → ligamentum teres hepatis (Note: contained in falciform ligament.)

FETAL ERYTHROPOIESIS

Organ Involvement

Fetal erythrocytes are produced in different locations throughout the life of the fetus.

- **Y**olk sac (3–8 weeks) during organogenesis
- **L**iver (7 weeks–birth)
- **S**pleen (9–28 weeks)
- **B**one marrow (22 weeks–adult axial skeleton [pelvis, ribs, sternum, vertebrae] and long bones' proximal epiphyses)

Hemoglobin

Fetal hemoglobin consists of two alpha subunits and two gamma subunits (α_2 and γ_2). Because fetal hemoglobin has a higher affinity for oxygen due to its lower affinity for 2,3-bisphosphoglycerate (2,3-BPG) than does adult hemoglobin, the transfer of oxygen across the placenta from maternal to fetal circulation is ensured.

After birth, there is a gradual decrease in red cell production, caused by increased oxygenation of systemic circulation, and a switch from fetal to adult hemoglobin (consists of two alpha and two beta subunits). This results in a physiologic anemia that nadirs around 4–8 weeks of life before a new steady-state production of adult hemoglobin is established.

FETAL CIRCULATION

The fetal circulation is designed to meet the needs of the growing fetus without utilizing the oxygenating capacity of the lungs, which are filled with amniotic fluid in utero. To accomplish this, oxygenated blood from the mother travels from the placenta via the **umbilical vein** to the fetal systemic circulation, and deoxygenated blood from the fetus travels back to the placenta via the **umbilical arteries** (Figure 1-9). There are three important shunts in the fetal circulation:

1. Blood entering the fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC, bypassing hepatic circulation.
2. Most of the highly oxygenated blood reaching the heart via the IVC is directed through the **foramen ovale** and pumped into the aorta to supply the head and body.
3. Deoxygenated blood from the SVC passes through the right atrium → right ventricle → main pulmonary artery → **patent ductus arteriosus (PDA)** → descending aorta. This shunt via the PDA can occur because of the high fetal pulmonary artery resistance (due in part to low fetal oxygen tension and high concentration of circulating vasodilators like nitric oxide and prostaglandins).

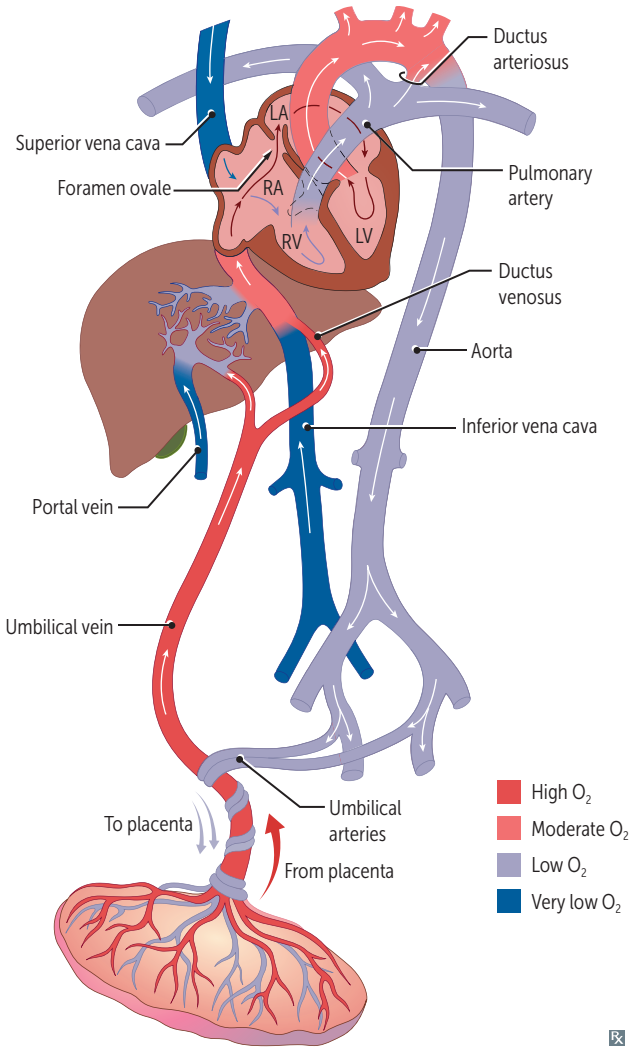


FIGURE 1-9. Fetal circulation. Most of the oxygenated blood reaching the heart via the umbilical vein (O_2 saturation ~ 80%) and inferior vena cava is diverted through the foramen ovale into the left atrium and pumped out into aortic arch vessels to the head, neck, and upper extremities (O_2 saturation ~ 60%), while deoxygenated blood returned via the superior vena cava is mostly pumped through the pulmonary artery and ductus arteriosus to the feet and the umbilical arteries.

After birth, as the neonate begins to breathe, the pulmonary arterial resistance decreases due to increased oxygen tension and decreased circulating vasodilators. For the first time, pressures in the left heart exceed pressures in the right heart. The increase in left atrial pressure forces the septum primum against the septum secundum, closing the foramen ovale (now called **fossa ovalis**). Closure of the ductus arteriosus and ductus venosus is mediated by falling levels of prostaglandins due to increased oxygen content in the circulation.

KEY FACT

In cardiomegaly the apex is shifted laterally; therefore the point of maximal impulse (PMI) is palpated more lateral than the midclavicular line.

Anatomy

SURFACES AND BORDERS OF THE HEART

- The **anterior (sternal) surface** is formed by the RV (Figure 1-10A).
- The **posterior surface** is formed by the LA and is in close proximity to the esophagus.
- The **right border** is formed by the right atrium.

QUESTION

An 18-year-old man is stabbed with a knife just to the right of the sternum between the fourth and fifth ribs. Which cardiac structure is penetrated by the knife?

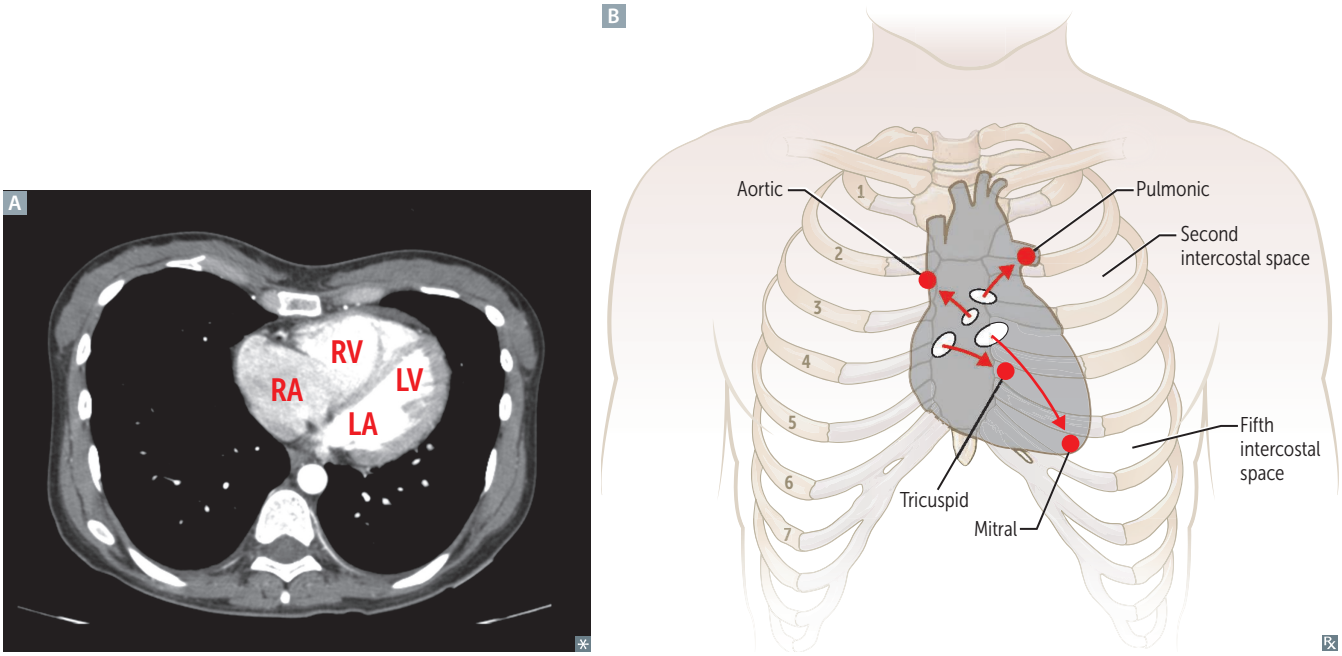


FIGURE 1-10. Anatomic relationships of the heart. A Axial CT of the heart. B Anatomic relationship of valves in the heart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

CLINICAL CORRELATION

Aortic stenosis (AS) and hypertrophic obstructive cardiomyopathy (HOCM) both produce **systolic crescendo-decrescendo murmurs.** In AS, the murmur is best heard in the right upper sternal border and radiates to the carotids and/or cardiac apex. In HOCM, the murmur does not typically radiate and is best heard at the left sternal border; it also increases in intensity with Valsalva (AS murmur decreases in intensity with Valsalva).

CLINICAL CORRELATION

Mitral regurgitation (MR) causes a **holosystolic blowing murmur,** heard best at the cardiac apex. It can sometimes be confused with tricuspid regurgitation; however, the murmur of tricuspid regurgitation becomes louder with inspiration.

ANSWER

The right atrium forms the right border of the heart. Note that the right ventricle forms the anterior portion of the heart to the left of the sternum.

- The **left border** is formed by the LA and LV.
- The **apex** is formed by the LV.

RELATIONSHIPS OF THE HEART AND GREAT VESSELS

- The **right border** is formed by the right atrium and is located between the third and sixth ribs along the right sternal border.
- The **left border** is formed by the left ventricle and is located between the third and sixth ribs between the midclavicular line and left sternal border.
- The apex is located at the fifth intercostal space, midclavicular line. The point of maximal impulse (PMI) is normally palpated here.
- The **aortic arch** is located at the level of the sternal notch, corresponding to vertebral level T2.
- The **superior vena cava (SVC)** enters the RA at the level of the third rib.

HEART VALVES AND SITES OF AUSCULTATION

The four heart valves are the **aortic, pulmonic, mitral,** and **tricuspid valves** (Table 1-3). It is important to understand how valve movement relates to the cardiac cycle (discussed in The Cardiac Cycle).

Many cardiac diseases and valvular lesions result in abnormal heart sounds. Abnormal heart sounds are due to aberrant blood flow; therefore, the site of auscultation of a particular valve is downstream to the direction of flow through that valve (Figure 1-10B).

LAYERS OF THE HEART

The heart is composed of three layers: **endocardium, myocardium,** and **pericardium** (Figure 1-11).

TABLE 1-3. Characteristics of Heart Valves

VALVE	LOCATION	STRUCTURE	SITE OF AUSCULTATION	PHASE WHEN VALVE IS OPEN
Aortic	Between LV and aorta	Semilunar (3 cusps)	Right second IS at the SB	Systole
Pulmonic	Between RV and pulmonary trunk	Semilunar (3 cusps)	Left second IS at the SB	Systole
Mitral	Between LA and LV	Bicuspid	Left fifth IS at the midclavicular line	Diastole
Tricuspid	Between RA and RV	Tricuspid	Left fifth IS at the SB	Diastole

IS, intercostal space; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SB, sternal border.

Endocardium

The endocardium is the innermost layer and contacts the blood in the heart chambers. It is composed of simple squamous epithelium (endothelium) and underlying connective tissue.

Myocardium

The myocardium is the middle and thickest layer composed of myocytes, the contractile cells responsible for pumping blood through the heart.

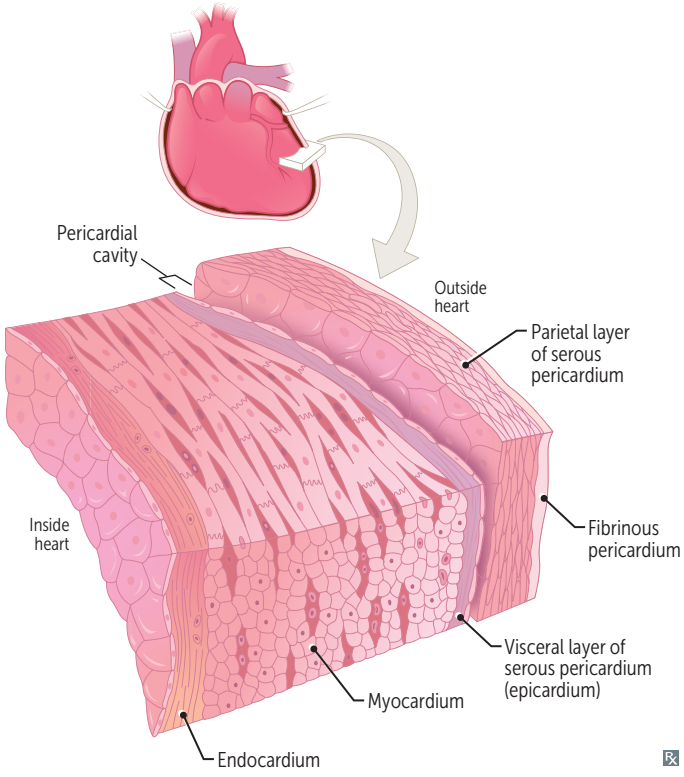


FIGURE 1-11. Layers of the heart. The three layers are epicardium, myocardium, and endocardium. The pericardial space is lined by a visceral and parietal layer of pericardium that encloses a thin layer of serous fluid.

MNEMONIC

All **P**atients **T**ake **M**eds
Aortic
Pulmonic
Tricuspid
Mitral

CLINICAL CORRELATION

Cardiac tamponade is the compression of the heart by fluid (ie, blood) in the pericardial sac, leading to decreased cardiac output (CO). Classic signs are distended neck veins, hypotension, and muffled heart sounds (Beck triad). Treatment is pericardiocentesis.

CLINICAL CORRELATION

Hypertrophy of the myocardium occurs in hypertrophic obstructive cardiomyopathy (HOCM) and can result in sudden death due to ventricular arrythmias from poorly functional myocytes.

QUESTION

Which heart vessel carries the most deoxygenated blood?

CLINICAL CORRELATION

Transmural infarction affects all three layers of the heart. **Subendocardial** infarction affects only the endocardium, which is furthest from the coronary artery and most susceptible to ischemia and necrosis.

CLINICAL CORRELATION

Pericarditis is inflammation of the pericardium; causes of which vary and include systemic lupus erythematosus (SLE), rheumatoid arthritis, myocardial infarction (MI), tuberculosis (TB), and malignancy. Findings include chest pain and friction rub on auscultation, and the ECG shows diffuse ST elevations, often with PR segment depression, in all leads.

KEY FACT

Tachycardia shortens diastole so the heart receives less blood supply.

A ANSWER

Coronary sinus. Located in the posterior of the heart at the junction between the RA and RV (not shown in Figure 1-12). Drains coronary arteries and empties directly into the RA, along with the SVC and IVC. Has the lowest O_2 saturation (30%) in the body.

Pericardium

The pericardium is composed of two layers: the outer **fibrous pericardium** and the inner **serous pericardium.** It covers the heart and proximal portion of the great vessels.

- **Fibrous pericardium** is the tough connective tissue that tethers the heart in place via its connections to the sternum anteriorly and the central tendon of the diaphragm inferiorly.
- **Serous pericardium** comprises two layers: the parietal layer and the visceral layer.
  - The parietal layer is continuous with the internal aspect of the fibrous pericardium.
  - The visceral layer, also known as the **epicardium,** is the thin innermost layer of the pericardium. This layer contains the major branches of the coronary arteries.

CORONARY ARTERY ANATOMY

Major Branches

The coronary arteries arise from the proximal portion of the aorta (the aorta's first branches) as the **right coronary artery (RCA)** and the **left coronary artery (LCA)** (Figure 1-12). These vessels lie just deep to the epicardium on the surface of the heart.

The heart receives a dual blood supply: The **epicardium** and **myocardium** are supplied by the **coronary arteries** and their branches, whereas the **endocardium** receives O_2 and nutrients from distal branches of the coronary arteries and has direct contact with blood inside the heart chambers.

When flow through a coronary artery is compromised, the subendocardial tissue is most vulnerable to ischemic injury because it lies in the zone farthest from either blood supply.

Flow through the coronary arteries occurs mainly during diastole. The contraction of the myocardium during systole increases external pressure on the vessels and inhibits blood flow through them.

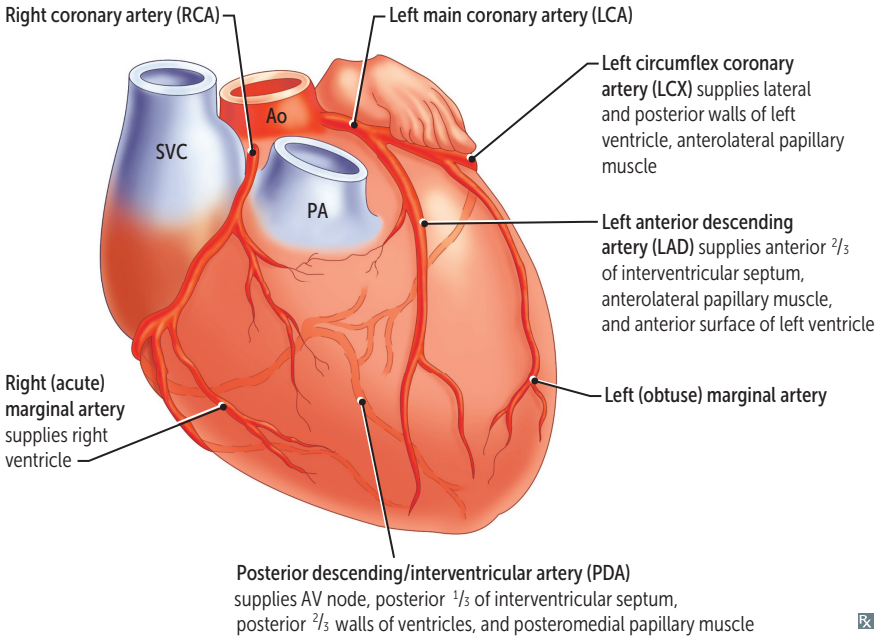


FIGURE 1-12. Coronary artery circulation. Ao, aorta; PA, pulmonary artery; SVC, superior vena cava.

Major branches of the LCA are the **left anterior descending artery (LAD)** and **left circumflex artery.**

Major branches of the RCA are the **marginal artery** and the **posterior descending artery.**

Dominant Circulation

The coronary artery that supplies the posterior descending artery (PDA) is considered the dominant artery of the heart.

- Right-dominant circulation = 85% (PDA arises from RCA.)
- Left-dominant circulation = 8% (PDA arises from left circumflex coronary artery [LCX].)
- Co-dominant circulation = 7% (PDA arises from RCA and LCX.)

CLINICAL CORRELATION

Acute MI of the inferior portion of the heart (RV) is associated with characteristic ECG findings of ST-segment elevation in leads II, III, and aVF.

Acute Coronary Syndrome

Acute coronary syndrome (ACS) describes a spectrum of serious clinical diagnoses (unstable angina, non-ST elevation myocardial infarction [NSTEMI], and ST-elevation myocardial infarction [STEMI]) that affect individuals with coronary artery disease. The most common cause of ACS is occlusion due to thrombus from an atherosclerotic plaque (Figure 1-13).

The coronary artery **most commonly occluded** (40–50%) is the **LAD,** followed by the RCA, and then the left circumflex. STEMI results in characteristic ECG changes demonstrated in Figure 1-14 and Table 1-4.

CONDUCTION SYSTEM

The cardiac conduction system is responsible for distributing electrical impulses throughout the heart so that the atria and ventricles function in concert as an effective pump. The sequence of electrical activation in the heart is outlined below and in Figure 1-15:

1. **Sinoatrial (SA) node:** Called the **native pacemaker** of the heart, the SA node is where the electrical impulse is initiated. It is located at the junction of RA and SVC and contains specialized myocytes that have the ability to depolarize spontaneously **(automaticity)** at a regular rate of 60–100 beats per minute at rest.
2. The electrical impulse from the SA node travels through both atria (right → left) until it eventually reaches the **AV node.**

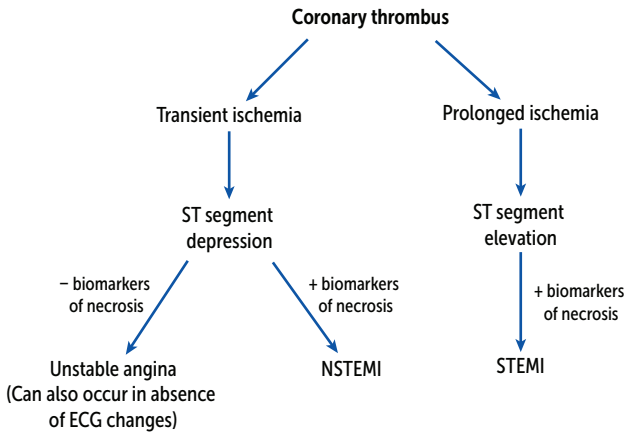


FIGURE 1-13. Spectrum of acute coronary syndrome. A coronary thrombus, depending on how occlusive it is and/or how much ischemia it causes, can lead to unstable angina, non-ST elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI), which are distinguished by ECG findings (ST segment elevation/depression) and biomarkers of necrosis (eg, troponins).

QUESTION

A 74-year-old man presents with acute chest pain, shortness of breath, and severe bradycardia, and the ECG in Figure 1-14. What coronary artery branch is occluded in this patient presenting with an MI?

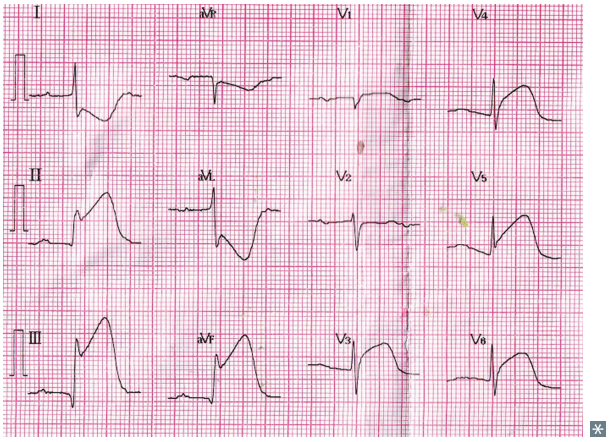


FIGURE 1-14. ECG findings in myocardial infarction. ST-segment elevation in the inferior (II, III, and aVF) and anterior (V_3–V_6) leads.

CLINICAL CORRELATION

Conduction block is a type of arrhythmia that occurs when there is cellular damage to conducting cells, outlined in Figure 1-15. Complete AV block, for example, can lead to no conduction between atria and ventricles, often requiring a pacemaker.

3. **Atrioventricular (AV) node:** Located in the posteroinferior part of the interatrial septum near the coronary sinus, the AV node delays conduction from the atria to the ventricles (100 msec delay) to allow time for the atria to depolarize and fully empty their contents into the ventricles before ventricular contraction.
4. After a brief delay in the AV node, the electrical impulse spreads through the ventricular conduction system, which contains specialized myocytes from below the AV node to walls of both ventricles: **Bundle of His** → divides into the **right and left bundle branches** along the interventricular septum (note that the **left bundle branch** splits into the **left anterior** and **left posterior fascicles**) → bundles and fascicles terminate in specialized conducting fibers termed **Purkinje fibers** in the walls of both ventricles to distribute the electrical impulse to allow for full ventricular contraction.

Physiology

The cardiovascular (CV) system, which can be modeled as a pump (heart) and a set of tubes (blood vessels), distributes O_2, nutrients, and other substances to the tissues while removing metabolic by-products from the tissues.

CARDIAC ELECTROPHYSIOLOGY

To generate an electrical signal that can regularly contract the atria and ventricles, the heart contains two populations of cells: **conducting** and **contractile cells.** Conducting (nodal) myocytes form the specialized conduction pathway of the heart (SA node, AV node, bundle of His, bundle branches, Purkinje fibers). They have the ability to

TABLE 1-4. ECG Findings With ST Segment Elevation Myocardial Infarction (STEMI)

AREA OF INFARCT	CORONARY ARTERY INVOLVED	LEADS WITH ST ELEVATION
Inferior wall (RV)	RCA	II, III, aVF
Anterior wall (may include septum)	LAD	V_2, V_3
Lateral wall (LV)	Left circumflex	I, aVL, V_5, V_6

aVF, augmented voltage foot; aVL, augmented voltage left arm; LAD, left anterior descending; LV, left ventricle; RCA, right coronary artery; RV, right ventricle.

ANSWER

RCA. ST elevation in inferior leads (II, III, and aVF). Recall that RCA perfuses the AV node. Ischemia of the AV node can cause nodal dysfunction and result in bradycardia and various degrees of heart block.

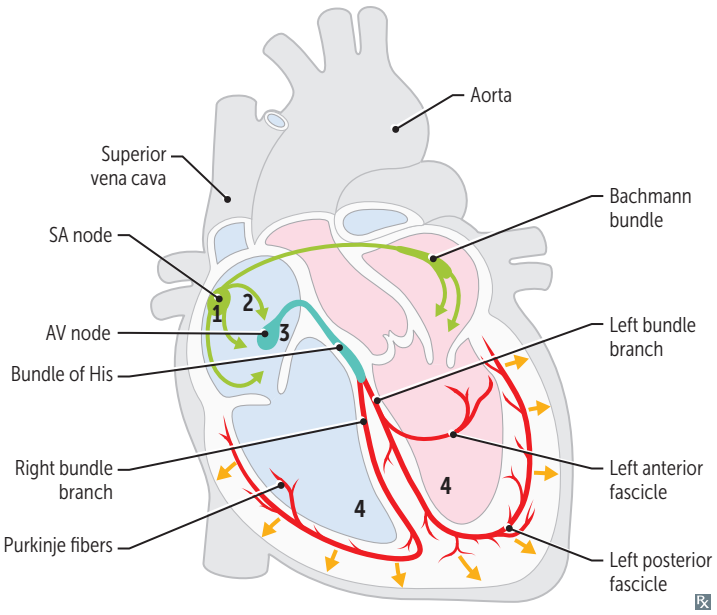


FIGURE 1-15. Anatomy of the conduction system in the heart.

spontaneously generate action potentials (APs). APs travel along the normal conduction pathway (Figure 1-15) to stimulate surrounding contractile myocytes via electrical gap junctions to contract and generate enough force to pump blood into the circulation.

Resting Membrane Potential

By convention, the resting membrane potential of a cell is measured in mV relative to the extracellular space. Excitable cells, like cardiac myocytes, neurons, and skeletal myocytes, have resting membrane potentials between –70 and –90 mV. The membrane potential (Vm) in all cells can be explained by:

- The relative conductance of the cell membrane for certain ions (eg, K^+, Na^+, Ca^{2+}). This determines which ion's equilibrium potential predominates. The membrane potential at any point in the AP is determined by the relative contribution of different ion conductances.
- The relative intracellular and extracellular concentrations of these ions.

At rest, the membrane conductance is higher for K^+ than it is for the other major ions (Na^+ or Ca^{2+}). This explains why the resting membrane potential is close to the equilibrium potential for K^+ (a function of the intracellular ($[K^+]_i$) and extracellular ($[K^+]_e$) potassium concentration gradient). Since $[K^+]_i >> [K^+]_e$, K^+ diffuses out of the cell and down its concentration gradient, causing the V_m to become more negative (losing positive charge to the outside). At a certain membrane potential, the net force driving K^+ along its electrochemical gradient equals the net concentration gradient driving ions across the membrane. This potential at which there is no net movement of ions across the membrane is the **equilibrium (or Nernst) potential (E_K)** and can be calculated:

$$E_K = \frac{-61}{z} \log \frac{[K^+]_i}{[K^+]_e}$$

(z = 1 because K^+ is monovalent)

If $[K^+]e$ = 4 mEq/L and $[K^+]i$ = 120 mEq/L, the membrane potential for K^+ = 91 mV, which closely approximates the resting membrane potential for a ventricular contractile myocyte (–90 mV). Notably, conducting myocytes (eg, SA and AV node) have a

KEY FACT

Membrane conductance describes the cell membrane's permeability to a particular ion. It is a function of whether the ion channels specific to a particular ion are open. Because an action potential triggers voltage-gated channels to open and close, ion conductance varies throughout an action potential.

KEY FACT

Inward current positive charge (eg, Ca^{2+}, K^+, Na^+) enters cell → depolarizes V_m (makes less negative).
Outward current positive charge (eg, K^+) leaves cell → hyperpolarizes V_m (makes more negative).

less-negative resting potential because of a higher conductance to Ca^{2+} and Na^+ at less-negative voltages due to spontaneous depolarization (see Cardiac Action Potentials below).

KEY FACT

The most important difference between fast- and slow-response cardiac action potentials is the ion responsible for the phase 0 upstroke:
Fast-response action potential = fast inward **Na^+ current**
Slow-response action potential = slow inward **Ca^{2+} current**

In contrast to K^+, since the [Na^+] is higher in the extracellular space, Na^+ tends to enter the cell and make the membrane potential more positive. The Na^+-K^+-ATPase pump maintains the ionic gradient across the cell membrane by pumping 3 Na^+ out for every 2 K^+ pumped in. This maintains the resting Na^+ and K^+ intracellular and extracellular concentration gradients (Figure 1-16).

Cardiac Action Potentials

Cardiac myocytes produce two types of action potentials (APs): fast response and slow response (Figure 1-17). These APs, which measure the electrical potential of the cell over time, differ in their shape and conduction velocity (Table 1-5).

Fast-Response (Ventricular) Action Potential

Fast-response APs occur in the atrial and ventricular myocytes, the bundle of His, and Purkinje fibers.

- Phase 0: Rapid upstroke and depolarization. Voltage-gated Na^+ channels open.
- Phase 1: Initial repolarization. Inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.
- Phase 2: Plateau. Ca^{2+} influx through voltage-gated **L-type** Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release of intracellular Ca^{2+} from sarcoplasmic reticulum and myocyte contraction.
- Phase 3: Repolarization. Massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels (via calcium-dependent inactivation).
- Phase 4: Resting potential. High K^+ permeability through K^+ channels.

FLASH FORWARD

The four classes of antiarrhythmia drugs target specific channels/receptors:
Class I: Na^+ channel blockers
Class II: β-Blockers
Class III: K^+ channel blockers
Class IV: Ca^{2+} channel blockers

Slow-Response (Pacemaker) Action Potential

Slow-response APs occur in the SA and AV nodes.

- Phase 0: Upstroke (less rapid and steep than fast-response AP) and depolarization. Opening of voltage-gated **T-type** Ca^{2+} channels. A greater proportion of fast voltage-gated Na^+ channels are inactivated in pacemaker cells (they have a less negative resting membrane voltage than ventricular myocytes). In the AV node, this results in a slow conduction velocity to prolong transmission from atria to ventricles.
- Phase 1: Not present.
- Phase 2: Not present (no plateau).

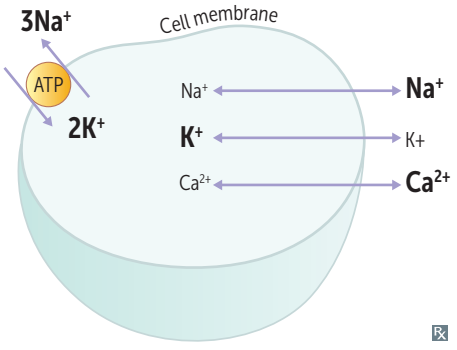


FIGURE 1-16. Intracellular and extracellular concentrations of Ca^{2+}, Na^+, and K^+ in mEq/L. The ATP-powered Na^+/K^+ pump maintains the baseline membrane potential, which is largely determined by [K^+].

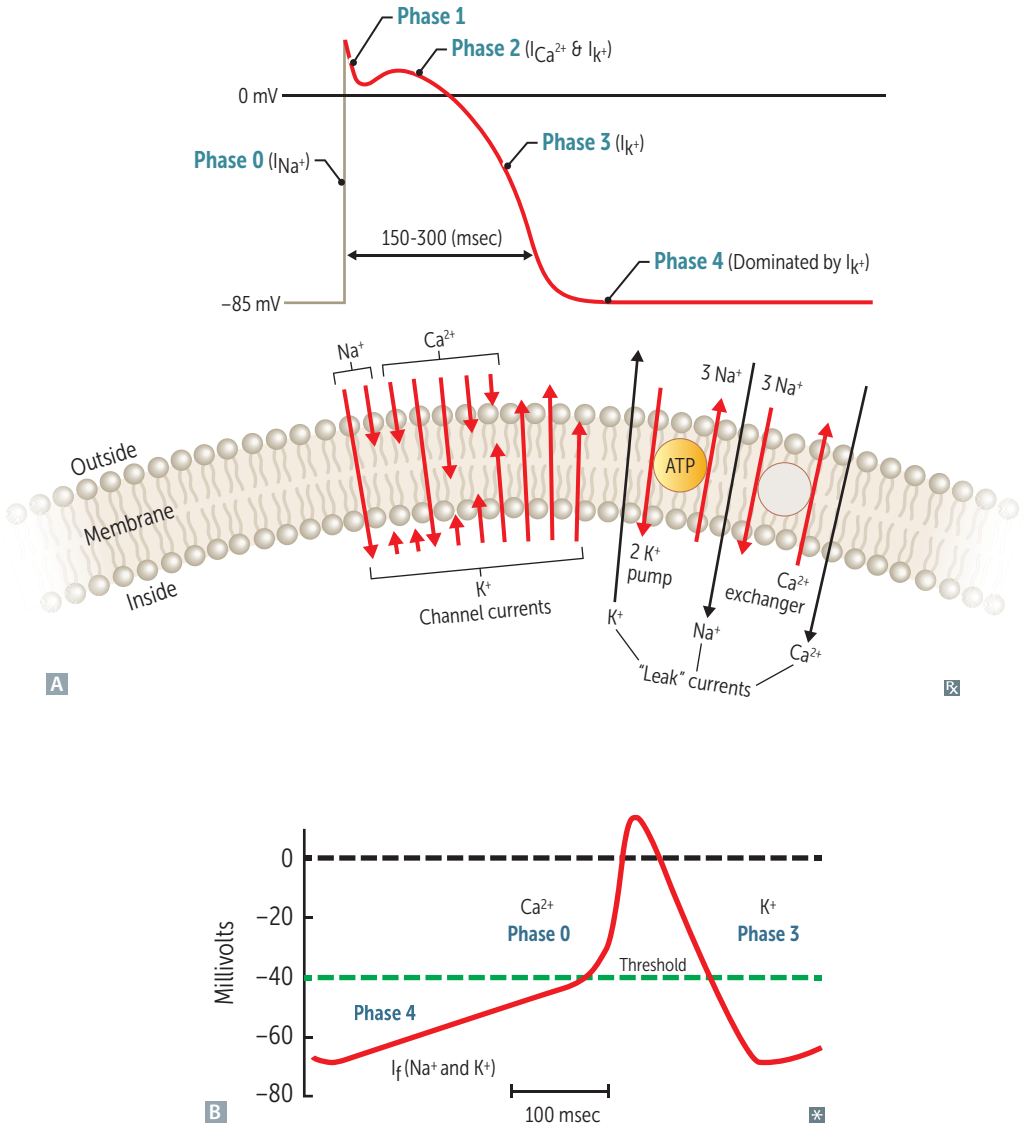


FIGURE 1-17. Fast response A and slow response B cardiac action potentials. I_X denotes the current (ie, flow of charge) of the specified ion (x) through the ion channel in the direction noted. Note that for the fast response action potential, the AP duration (150–300 msec) varies by location of conducting pathways (Purkinje fibers > ventricle > atria).

- Phase 3: Repolarization. Inactivation of the voltage-gated Ca^{2+} channels and increased K^+ conductance causes K^+ efflux.
- Phase 4: Slow diastolic depolarization. Membrane potential spontaneously depolarizes as Na^+ conductance increases through **I(f) "funny" Na^+ channels.** Accounts for the automaticity of the SA and AV nodes.

KEY FACT

"Funny" Na^+ channels are funny because, unlike fast-acting voltage-gated Na^+ channels activated by depolarization, funny Na^+ channels are activated by **hyperpolarization.**

Cardiac Pacemakers

Myocytes in the SA node, AV node, bundle of His, and Purkinje system all have the capacity to act as pacemakers of the heart, and each has different intrinsic firing rates **(automaticity):**

- SA node: 60–100 bpm
- AV node and proximal bundle of His: 50–60 bpm
- Purkinje cells: 30–40 bpm

The myocytes with the fastest intrinsic firing rates (ie, SA node) are the **native pacemakers** of the heart because they **overdrive suppress** the **latent pacemakers** (ie, AV node,

TABLE 1-5. Comparison of Slow and Fast Action Potentials

	SLOW PACEMAKER ACTION POTENTIAL	FAST ACTION POTENTIAL
Length of AP	150 ms (SA, atria), 250–300 ms (AV, ventricular)	100 ms
Conduction velocity	0.01–0.10 m/sec	0.3–3.0 m/sec
Tissues involved	SA and AV nodes	Atria, ventricles, bundle of His, Purkinje fibers
Phases	0. Increased $I_{Ca^{2+}}$	0. Increased $I_{Na^{+}}$
	1. Increased $I_{K^{+}}$	1. Decreased $I_{Na^{+}}$, increased $I_{K^{+}}$
	4. Increased $I_{f(Na^{+})}$	2. Increased $I_{Ca^{2+}}$, increased $I_{K^{+}}$
		3. Decreased $I_{Ca^{2+}}$, increased $I_{K^{+}}$
Targeting antiarrhythmics	Class II β-blockers (phase 4), class IV Ca channel blockers (phase 0)	Class Ia, Ib, Ic (phase 0), class III (phase 3)

AP, action potential; AV, atrioventricular; SA, sinoatrial.

CLINICAL CORRELATION

Electrolyte changes can also affect the shape of APs. **Calcium gluconate,** for example, is often administered to counteract the effects of hyperkalemia. Persistent hyperkalemia causes depolarization of the membrane potential and inactivates Na^{+} channels, ultimately decreasing membrane excitability and predisposing to life-threatening arrhythmias. Calcium reverses this effect and restores membrane potential by a mechanism that is not fully understood.

bundle of His, Purkinje system) to maintain a regular rate and rhythm. If the SA node fails to fire, the next fastest pacemaker cells (ie, AV node) will take over, and if the AV node fails to fire, the next fastest pacemaker cells (bundle of His and Purkinje cells) will take over.

Although pacemaker cells have automaticity, autonomic nervous system input (along with drugs that mimic their effects) can affect the heart rate (HR). Table 1-6 highlights the effect of sympathetic and parasympathetic stimulation on portions of the pacemaker action potential to increase and decrease heart rate, respectively.

Conduction Velocity

Conduction velocity (m/sec) is the speed at which APs travel through the myocardium. The speed depends on the size of inward current during the AP upstroke (phase 0); the

TABLE 1-6. Effect of Autonomic Nervous System and Drugs on Pacemaker Action Potentials

STIMULATION	EFFECT ON HEART RATE	EFFECT ON RESTING MEMBRANE POTENTIAL	EFFECT ON SLOPE OF PHASE 4 DEPOLARIZATION	EFFECT ON THRESHOLD POTENTIAL
↑ Acetylcholine (parasympathetic ANS) ↑ Adenosine ↑ β-blockers	↓	More negative	Decreased (due to ↓ I_f)	More positive
↑ Catecholamines (sympathetic ANS, caffeine, cocaine)	↑	More positive	Increased (due to ↑ I_f)	More negative

ANS, autonomic nervous system; HR, heart rate.

larger the inward current, the faster the electrical impulse can spread to neighboring myocytes via gap junctions. A point that often causes confusion: AP duration (from depolarization to repolarization) does not impact conduction velocity, because conduction velocity measures how fast APs spread **between** cells (a function of inward current). Conduction velocity is fastest in the Purkinje system (2–4 m/sec) and slowest in the AV node (0.01–0.05 m/sec). A slower conduction velocity in the AV node means that the excitation of the ventricles is delayed. The AV nodal delay enables the atria to empty fully into the ventricles prior to depolarization of the ventricles, thus improving ventricular filling and increasing cardiac output in a given beat. Fast conduction velocity in the Purkinje fibers ensures uniform and efficient ventricular contraction to maintain cardiac output.

MNEMONIC

Park **AT Vent**ura **AV**enue:
Purkinje > **AT**rial myocytes >
Ventricular myocytes > **AV** node

KEY FACT

Conduction velocity through the AV node is affected by:

- Sympathetic nervous system (SNS): ↑ conduction leads to ↓ PR interval
- Parasympathetic nervous system (PNS): ↓ conduction leads to ↑ PR interval

Refractory Period

The duration of cardiac myocyte APs (150–300 msec) is longer than the duration of neuron and skeletal myocyte APs (1–2 msec). Since duration of an AP is directly proportional to duration of its **refractory period,** it follows that cardiac myocytes have long refractory periods to ensure the heart has enough time to fill during diastole and to prevent tetany.

The underlying basis of the refractory period is **closure of Na^+ channel inactivation gates** (Figure 1-18). Depolarization activates Na^+ channel gates to open and simultaneously initiates Na^+ channel inactivation gates to close (at a slower rate), which results in termination of the upstroke (phase 0). Na^+ channel inactivation gates progressively reopen during repolarization, resulting in three degrees of excitability during the refractory period (Figure 1-19):

- **Absolute:** Begins at phase 0 (upstroke) to the end of phase 2 (plateau). "Absolutely" no AP can be generated, regardless of amount of inward current, because nearly all Na^+ inactivation gates are closed.
- **Effective:** Begins at phase 0 (upstroke) to the beginning of phase 3 (start of repolarization). An "effective" AP (ie, an AP that can conduct to neighboring cells) cannot be generated because not enough Na^+ inactivation gates have yet recovered.
- **Relative:** Begins at end of absolute refractory period to approximately end of phase 3 (repolarization). Because more Na^+ inactivation channels recover during this period, a "relatively" larger-than-normal stimulus is able to generate a second AP.

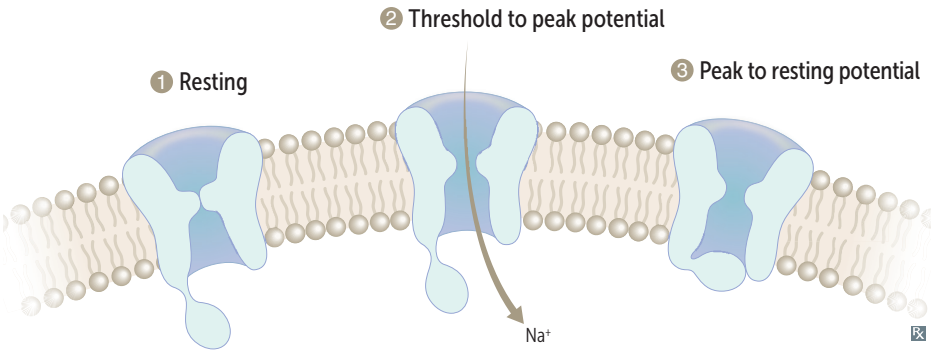


FIGURE 1-18. Voltage-gated inactivation and activation gates. (1) At rest, the sodium activation gate is closed and sodium inactivation gate is open. (2) Depolarization causes the voltage-gated sodium activation gate to open. (3) As depolarization causes the cell to reach its maximum cell potential, it triggers the voltage-gated sodium inactivation gate to close, making the cell refractory to additional depolarizing stimuli. The inactivation gate reopens during repolarization as the cell returns to its resting membrane potential (1).

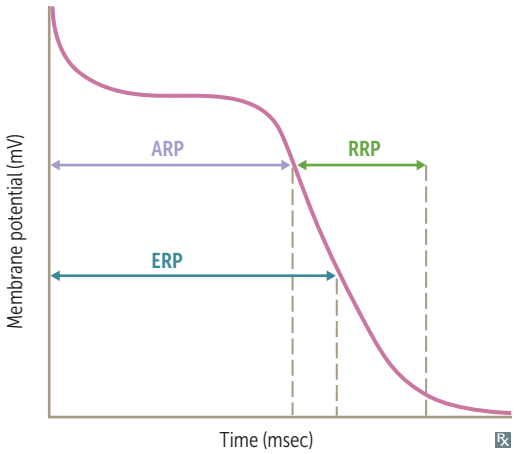


FIGURE 1-19. Absolute (ARP), effective (ERP), and relative (RRP) refractory periods in the ventricle. Sodium inactivation gates reopen with increasing time of phase 3 (repolarization), resulting in these three degrees of excitability. Note that ARP and ERP both start at phase 0 and RRP starts at the end of ARP.

CARDIAC MUSCLE AND CONTRACTION

Contraction of the cardiac muscle cell is initiated by the AP signal acting on intracellular organelles to evoke the generation of tension and shortening of the cell. These APs are profoundly different from those of skeletal muscle cells. Cardiac and skeletal muscles differ physiologically (Table 1-7).

Excitation-Contraction Coupling

Excitation-contraction coupling occurs for all excitable cells and refers to the ability of an AP to cause contractile force in the cell. Ca^{2+} facilitates generation of contractile force in all three types of muscle in the body (skeletal, cardiac, smooth muscle), but the path that causes APs to generate intracellular Ca^{2+} varies for different cell types.

In contrast to skeletal myocytes, for example, cardiac myocytes use Ca^{2+} influx through **L-type Ca^{+} channels** during phase 2 of the AP to directly trigger more Ca^{2+} release from intracellular stores (**Ca^{2+}-induced Ca^{2+} release**). Skeletal myocytes lack Ca^{2+} influx during the AP (no phase 2) and thus mechanically couple voltage-gated chan-

TABLE 1-7. Characteristics of Cardiac and Skeletal Myocytes

MEMBRANE CHARACTERISTIC	CARDIAC MYOCYTES	SKELETAL MYOCYTES
Duration of AP	150–300 msec	1–2 msec
Plateau (phase 2 of AP) of non-pacemaker cells	Present (Ca^{2+} ions involved in cell depolarization)	Absent (no Ca^{2+} involved in cell depolarization)
Automaticity	Present in conducting cells	Absent
Gap junctions	Present	Absent
Mitochondria	↑↑↑	↑
Generation of contractile force	Increase in the individual fiber contractility	Increase in number of skeletal muscle fibers activated

AP, action potential.

nels activated by the AP to release Ca^{2+} inside the cell. The downstream mechanism of Ca^{2+}-generating contractile force is similar for skeletal and cardiac myocytes.

Excitation-contraction coupling depends on several structures in the cardiac myocyte (see Figure 1-20) that coordinate the contraction response to the cardiac AP:

- **Sarcomere:** Smallest contractile unit of cardiac muscle. Note that each cardiac myocyte contains multiple **myofibrils** that are composed of repeating sarcomere units. Each sarcomere unit is composed of thick (myosin) and thin (actin, tropomyosin, troponin) fibrous proteins that slide against each other, facilitating muscular contraction and relaxation. When viewed under a microscope, these filaments form dark and light bands that have been given different names (Figure 1-20):
  - I band: Contains actin. Shortens with contraction.
  - A band: Contains myosin. Length unchanged with contraction.
  - H band: Contains myosin. Shortens with contraction.
  - Z line: Marks borders of the sarcomere. Z lines come closer together with contraction.
  - M line: Marks the center of the sarcomere and midpoint of the thick filaments. Location unchanged with contraction.
- **T tubules:** Parts of the cell membrane that invaginate at the Z lines. They carry APs into the cell interior.
- **Sarcoplasmic reticulum:** Intracellular site of storage and release of Ca^{2+}, which facilitates Ca^{2+}-induced Ca^{2+} release.
- **Intercalated disks:** Located at the ends of cells (not shown in Figure 1-20). Mediate adhesion between cells.
- **Gap junctions:** Occur at the intercalated disks. Provide a path of low resistance for APs to rapidly spread between cells.

KEY FACT

During contraction, the H, I, and Z bands shorten. Only the A band stays constant throughout the cycle.

MNEMONIC

HIZ shrinkage. **A** band is **A**lways the same length.

Myocardial Contraction and Relaxation

The cardiac myocyte translates the electrical signal (AP) into a physical response (contraction) through the following steps: Extracellular Ca^{2+} enters myocardial cell → Ca^{2+} induces intracellular Ca^{2+} release → myocardial contraction, and finally myocardial relaxation.

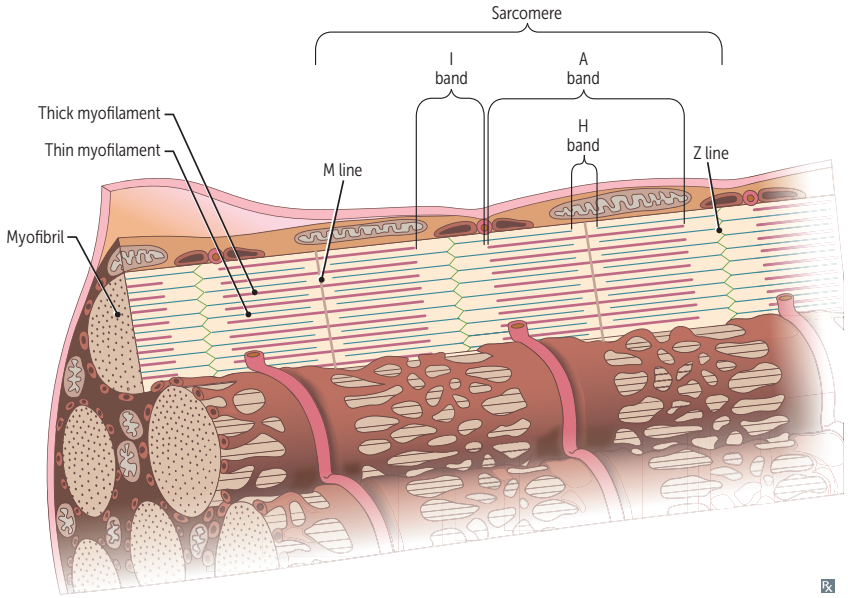


FIGURE 1-20. Schematic of the smallest contractile unit of a myocyte, the sarcomere. Labelled bands correspond to segments of thick (myosin) and thin (actin) filaments.

KEY FACT

↑ Ca^{2+} inward current during plateau of AP → ↑ intracellular [Ca^{2+}] → contractility (inotropy) in cardiac myocyte

KEY FACT

The contractility (inotropy) that can be generated by cardiac muscle is directly proportional to intracellular [Ca^{2+}].

- **Influx of extracellular Ca^{2+} into myocardial cells:** Action potential spreads along the cell membrane into the T tubules. During the plateau (phase 2) of the AP, extracellular Ca^{2+} enters the cell through voltage-gated Ca^{2+} (**L-type Ca^{2+}**) channels.
- **Ca^{2+}-induced Ca^{2+} release:** The influx of extracellular Ca^{2+} is not sufficient to induce muscle contraction. Therefore, extracellular Ca^{2+} binds to **ryanodine receptors** on the sarcoplasmic reticulum (SR), inducing a conformational change that releases Ca^{2+} from the SR.
- **Myocardial contraction:** Ca^{2+} release from the SR increases intracellular [Ca^{2+}] to cause sarcomere contraction according to the following steps (Figure 1-21):
  1. Released Ca^{2+} binds to **troponin C,** causing a conformational change that moves **tropomyosin** (normally blocks interaction between myosin and actin) away from the myosin-binding groove on actin filaments. Energy released from the hydrolysis of ATP → ADP + PO_4^{3-} is used to "cock" the myosin head into a high-energy state that can bind newly exposed actin filaments.
  2. The high-energy-state myosin binds to actin on the myosin-binding groove.
  3. The high-energy-state myosin uses its energy to undergo a "power stroke," in which it pulls the actin filaments attached to Z lines on either side of the M line toward the M line → sarcomere shortens → muscular contraction.
  4. Myosin will continue to stay bound to actin in its so-called "rigor conformation" until a new molecule of ATP attaches to the myosin head to facilitate detachment of myosin from actin.

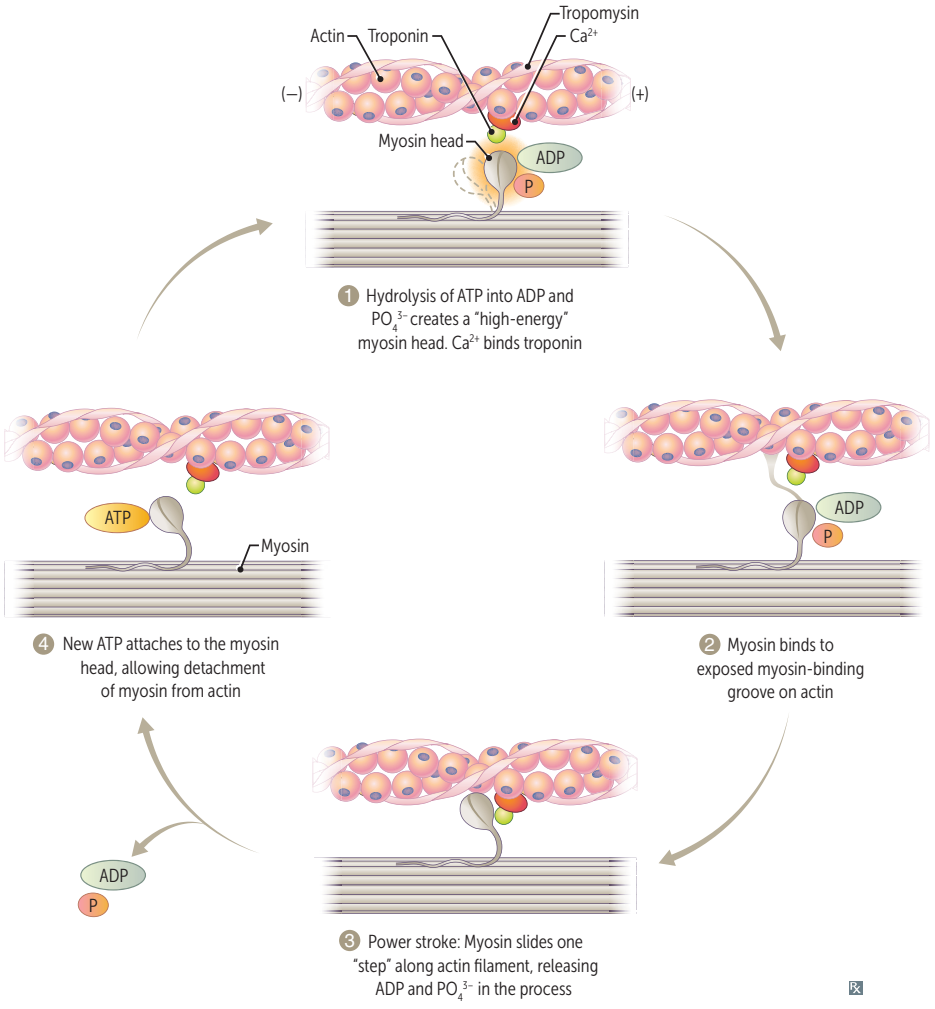


FIGURE 1-21. One cycle of skeletal muscle contraction at the level of the sarcomere. In the presence of Ca^{2+}, myosin moves along actin filaments via a "power stroke," fueled by the hydrolysis of ATP. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

These steps continue in a cycle when calcium is present. Each round of the cycle produces an additional "step" of myosin along actin, ultimately producing sufficient contractile force.

- **Myocardial relaxation:** Occurs when Ca^{2+} is pumped back into the SR via a Ca^{2+}-ATPase (SERCA) and expelled into the extracellular space with the help of a Ca^{2+}/Na^{+} pump (see Figure 1-17A). This reduces intracellular [Ca^{2+}] and removes Ca^{2+} from troponin, which terminates contraction of the sarcomere.

CARDIAC OUTPUT

The volume of blood pumped per minute from either ventricle, which should be equal in the absence of pathology, is known as **cardiac output (CO).** Normal resting CO is 4–8 L/min and can increase five- to sixfold during exercise. CO can be calculated using SV and HR (CO = SV × HR) or measured using Fick's O_2 method.

KEY FACT

Mean systemic pressure is increased by:
- Increased blood volume
- Decreased venous compliance (blood shifted from veins to arteries)
- Exercise (sympathetic stimulation)

Fick's Cardiac Output

Cardiac output is indirectly measured by measuring O_2 consumption. Based on conservation of mass, the amount of O_2 delivered to the body (product of CO and the difference in pulmonary artery and vein [O_2]) must equal O_2 consumed. The O_2 consumption for a 70-kg man is 250 mL/min, and the [O_2] in the pulmonary vein can be measured from a peripheral artery (no significant utilization of O_2 by tissues at this point), and the [O_2] in the pulmonary artery can be measured from the pulmonary artery or right ventricle.

$$O_2 \text{ delivered} - O_2 \text{ removed} = O_2 \text{ consumed}$$
$$CO \times ([O_2]pv - [O_2]pa) = O_2 \text{ consumed}$$
$$\text{Fick CO} = O_2 \text{ consumed}/([O_2]pv - [O_2]pa)$$

where

CO = cardiac output (L/min)
O_2 consumed = O_2 used by body (mL O_2/min) = 250 mL/min in a 70-kg man
[O_2]pa = O_2 in pulmonary artery (mL O_2/L blood)
[O_2]pv = O_2 in pulmonary vein (mL O_2/L blood)

KEY FACT

Factors that increase O_2 consumption:
- Increased afterload
- Increased contractility
- Increased HR
- Increased size of heart (increases radius → increases tension via LaPlace's law)

Stroke Volume

Stroke volume is the difference between end-diastolic volume and end-systolic volume, or the volume of blood ejected by the LV during a heartbeat. It varies directly as a function of contractility and preload and varies inversely with afterload. SV increases with increased preload, decreased afterload, or increased contractility. Other variables that affect SV and contractility are summarized in Table 1-8.

MNEMONIC

SV CAP
Stroke **V**olume affected by:
Contractility
Afterload
Preload

Ejection Fraction

The ejection fraction (EF) is the fraction of blood received by the LV (end-diastolic volume) that is ejected (SV) and directly reflects the state of contractility of the heart. A larger percentage of LV blood volume ejected (larger EF) reflects an increased contractile state.

$$EF = \frac{\text{stroke volume}}{\text{end-diastolic volume}} \times 100 \text{ (normal)} = 55\text{–}75\%)$$

KEY FACT

EF ↓ in systolic HF.
EF normal in diastolic HF.

$$SV = \frac{CO}{HR} = EDV - ESV$$

TABLE 1-8. Factors Affecting Contractility

CONTRACTILITY AND STROKE VOLUME ↑ "POSITIVE INOTROPIC EFFECT"	CONTRACTILITY AND STROKE VOLUME ↓ "NEGATIVE INOTROPIC EFFECT"
↑ **HR** (Ca^{2+} clearance is less efficient during shorter relaxation times → ↑ intracellular [Ca^{2+}])	↓ **HR** (Ca^{2+} clearance is more efficient during longer relaxation times → ↓ intracellular [Ca^{2+}])
Sympathetic stimulation (↑ catecholamines → stimulation of β_1 receptors → ↑ intracellular [Ca^{2+}] and ↑ activity of SR Ca^{2+} ATPase)	**Parasympathetic stimulation** (↑ ACh → stimulation of muscarinic receptors → ↓ intracellular [Ca^{2+}])
Digitalis (inhibition of myocardial cell membrane Na^+/K^+/ATPase → ↑ intracellular [Na^+] → decreased [Na^+] gradient across cell membrane → less intracellular Ca^{2+} removed by Na^+/Ca^{2+} exchanger → ↑ intracellular [Ca^{2+}])	β_1-blockade (↓ cAMP) HF with systolic dysfunction Acidosis Hypoxia/hypercapnia (↓ Po_2/↑ Pco_2) Non-dihydropyridine Ca^{2+} channel blockers

KEY FACT

In the absence of valvular pathology (eg, aortic stenosis), LV afterload during systole is proportional to systemic blood pressure (BP). In the RV, afterload (absent valvular pathology like pulmonic stenosis) is proportional to pulmonary artery pressure.

CLINICAL CORRELATION

LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.

FLASH FORWARD

- Vasodilators (eg, hydralazine) → ↓ afterload
- ACE inhibitors and ARBs → ↓ preload and afterload
- Chronic hypertension → ↑ afterload → LV hypertrophy (compensatory)

Determinants of Cardiac Output

Cardiac output is influenced by three major parameters affecting the left ventricle: **afterload, preload, and contractility.** As shown in Figure 1-22, these three parameters directly affect SV, which is a major determinant of CO in addition to HR.

Afterload

Afterload is the load that myocytes must contract against to generate CO. Afterload is more formally defined as **wall stress (σ)** on the LV during contraction (systole). Wall stress reflects the tensile force ("tension") per unit area the heart must generate during systole to eject blood across the aortic valve—it reflects the "load" the myocytes are contracting against. Laplace's law applied to the ventricle illustrates two key principles:

1. Wall stress **increases** with increased ventricular pressure (eg, hypertension) and increased ventricular radius (eg, dilated cardiomyopathy).
2. Wall stress **decreases** with increased ventricular thickness (eg, concentric hypertrophy of myocytes → more sarcomeres added in parallel per myocyte → reduced wall stress "felt" by each myocyte).

$$\sigma = \frac{P \times r}{2h}$$

where P is ventricular pressure, r is ventricular chamber radius, and h is ventricular wall thickness.

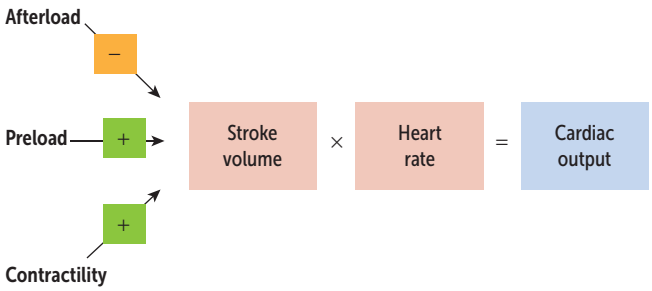


FIGURE 1-22. The determinants of cardiac output are stroke volume (SV) and heart rate. SV is directly proportional to contractility and preload and indirectly proportional to afterload.

Preload

The amount of "stretch" felt by the filled LV at the end of relaxation (diastole) before contraction (systole). In other words, it is the "wall stress" at the end of diastole (vs afterload, which is the wall stress during systole). Measurements of pressure or volume at end diastole are thus often used as proxies for preload: LV end-diastolic volume (LVEDV) and LV end-diastolic pressure (LVEDP).

KEY FACT

Preload is affected by ventricular **compliance** (ie, how "stiff" the ventricle is; more compliant → less ΔP for a given ΔV):

- ↓ compliance (eg, ventricular hypertrophy, diastolic heart failure) → ↓ **LVEDV** at a given EDP
- ↑ compliance (eg, dilated cardiomyopathy) → ↑ **LVEDV** at a given EDP

Length-Tension Relationship and Contractility (Inotropy)

Two mechanisms can influence force generation in cardiac muscle:

- Change in muscle fiber length
- Change in **contractility** or **inotropy** (independent of fiber length)

The first mechanism, involving change in muscle fiber length, is known as the **length-tension relationship** for myocytes. Derived from experimental observations, it reveals that sarcomere length impacts the force of contraction (Figure 1-23). At the optimal length, there is maximal actin-myosin overlap, which results in the maximum systolic contraction. Sarcomere length is directly related to **preload** (how "stretched out" ventricle is at end diastole).

KEY FACT

↓ **venous return** (eg, hemorrhage, vasodilation) → ↓ **preload**
↑ **venous return** (eg, administration of IV fluids, vasoconstriction) → ↑ **preload**

Contractility describes the amount of force generated by cardiac myocytes, **independent** of the intrinsic length-tension relationship for myocytes. Specifically, it describes how external factors, such as drugs (eg, calcium channel blockers [CCBs], β-blockers, digoxin), cell mediators (eg, catecholamines, intracellular [Ca^{2+}]), and pathologies (eg, CHF, hypoxia, acidosis) can influence contraction of the heart. Because increased contractile force of the heart → increased SV at a given LVEDV, the **ejection fraction** (= SV/LVEDV) can be a useful proxy in measuring how contractility ("inotropic state") of the heart changes with different interventions. Normal EF = 55–75%. Table 1-8 highlights important factors that affect contractility.

KEY FACT

Agents that ↑ contractility are referred to as positive inotropes. Agents that ↓ contractility are referred to as negative inotropes.

Frank-Starling Relationship

The greater the venous return, the greater the CO. In steady-state, the Frank-Starling principle ensures that venous return equals CO. It is one of the fundamental principles in cardiac physiology and is simply the **length-tension relationship** applied to ventricles. Since the "length" of a ventricle is proportional to **preload** (**LVEDV** or **LVEDP**) just before contraction, and the "tension" generated is proportional to measurable proxies of pressure generated in the LV (**CO** or **SV**), a curve with these axes (similar to the one drawn in Figure 1-23, notably without the descending limb) is often drawn to illustrate the Frank-Starling "curve" (Figure 1-24).

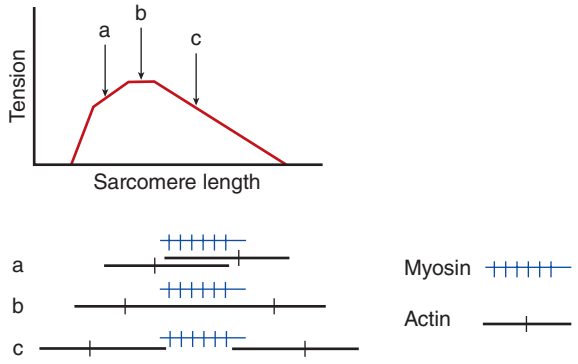


FIGURE 1-23. Effect of sarcomere length on the force of contraction. There is an ideal length that maximizes the overlap between actin and myosin (b) and maximizes tension generated. If the sarcomere is too short (a) or too long (c), the myosin and actin cannot interact optimally to produce maximal tension.

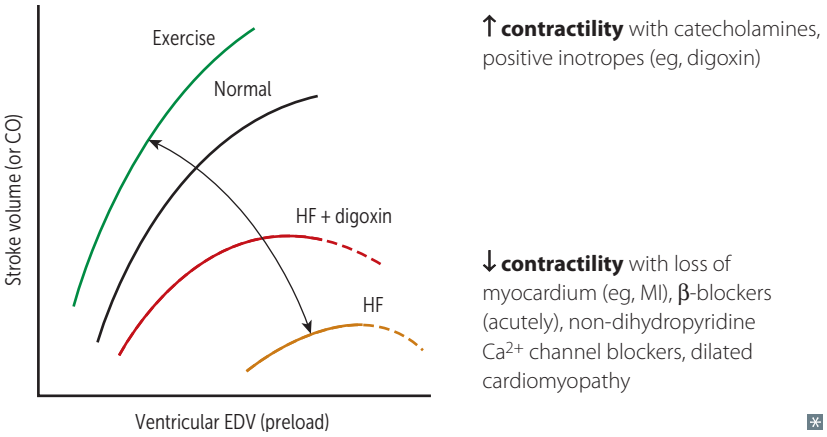


FIGURE 1-24. Frank-Starling curve. CO, cardiac output; EDV, end-diastolic volume; HF, heart failure.

The "normal" curve in Figure 1-24 illustrates that up to a certain point, force of systolic contraction (**SV** or **CO**) is directly proportional to the length of the cardiac muscle **(preload).** This rule holds up to a certain threshold preload. The heart at its strongest and contracting most vigorously can handle only so much venous return before it becomes overstretched. At a preload beyond this threshold value, actin-myosin overlap is no longer optimal, as cross-bridges cannot form. As a result, contractility decreases as preload continues to increase, resulting in the descending limb (not shown in Figure 1-24) of the Frank-Starling curve at excessively high preloads. Other curves in Figure 1-24 illustrate how the Frank-Starling curve shifts up or down with factors that increase and decrease contractility, respectively (Table 1-8). Specifically, at a given preload, **positive inotropic agents** increase ventricular function (↑ SV or CO), and **negative inotropic agents** decrease it.

KEY FACT

Increased venous return → increased cardiac output.

PRESSURE-VOLUME LOOPS

KEY FACT

Ventricular diastole begins with aortic valve closure and lasts through the mitral valve closure, whereas **ventricular systole** is defined as the part of the cardiac cycle from mitral valve closure to aortic valve closure.

Pressure-volume (PV) loops describe the relationship between LV volume and pressure during one full cardiac cycle, including contraction (systole) and relaxation (diastole) (Figure 1-25). PV loops are constructed in part by combining a pseudo–Frank-Starling curve (pressure-volume relationship in LV during systole) with another curve called the **compliance curve** (pressure-volume relationship in LV during diastole). The left ventricle PV loop for one full cardiac cycle has four main phases (contraction, ejection, relaxation, and filling), detailed below:

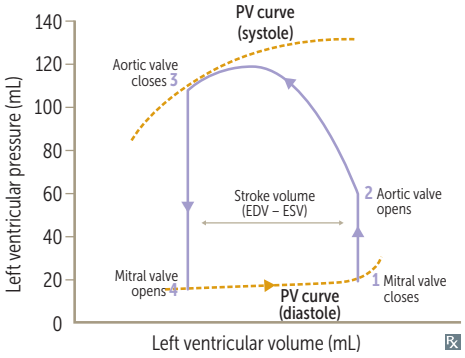


FIGURE 1-25. Left ventricular pressure-volume loop with overlayed systolic (top) and diastolic (bottom) PV curves. Note that the systolic PV curve is the principle behind the Frank-Starling curve. The diastolic PV curve is also referred to as the "compliance curve" for the ventricle during diastole. Increase in preload, for example, moves the PV loop "up" the compliance curve.

1 → 2: Isovolumetric Contraction (Systole)

Period between mitral valve (MV) closure, marking the end of diastole, and aortic valve (AoV) opening. Since the MV and AoV are closed, the LV is a closed chamber and contracts under a constant (isovolumetric) volume. No blood is ejected from the LV in this phase. The ventricular pressure continues to rise until LV pressure > aortic pressure.

2 → 3: Ventricular Ejection (Systole)

Eventually LV pressure > aortic pressure and AoV opens. Contraction of LV continues, allowing ejection of blood from the LV into the aorta. Volume ejected from the LV in this phase is the SV (width of the PV loop). When aortic pressure > LV pressure, AoV closes. Note that the maximum pressure generated during systole can be graphed directly on the pseudo–Frank-Starling curve.

3 → 4: Isovolumetric Relaxation (Diastole)

Period between AoV closing, marking the end of systole, and MV opening. Once again, the LV is a closed chamber and relaxes under a constant (isovolumetric) volume. No blood is ejected from the LV in this phase. The ventricular pressure continues to drop until LA pressure > LV pressure.

4 → 1: Ventricular Filling (Diastole)

When LA pressure > LV pressure, the MV opens. Blood moves from the LA (receiving venous return throughout cardiac cycle) into the LV. **Rapid filling** occurs just after MV opening caused by atrial contraction, followed by **slow filling** just before MV closing.

Variables That Affect PV Loops

PV loops are useful for visualizing changes in preload, afterload, or contractility. Increases or decreases in these parameters alter the shape of the PV loop; the effect of increasing these parameters on PV loops is highlighted in Figure 1-26.

CARDIAC AND VASCULAR FUNCTION CURVES

The cardiac and vascular function curves illustrate how CO and venous return change with respect to RA pressure or end-diastolic volume (EDV). It is important to understand that each curve goes in opposite directions (Figure 1-27) because, because each answers a different question:

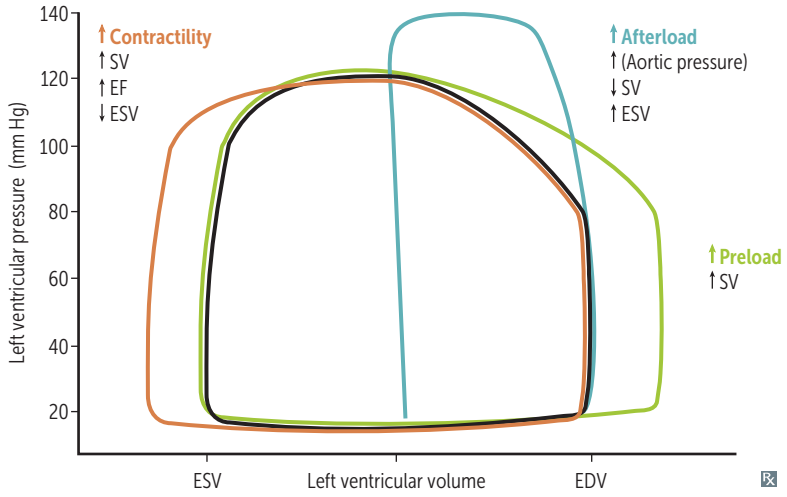
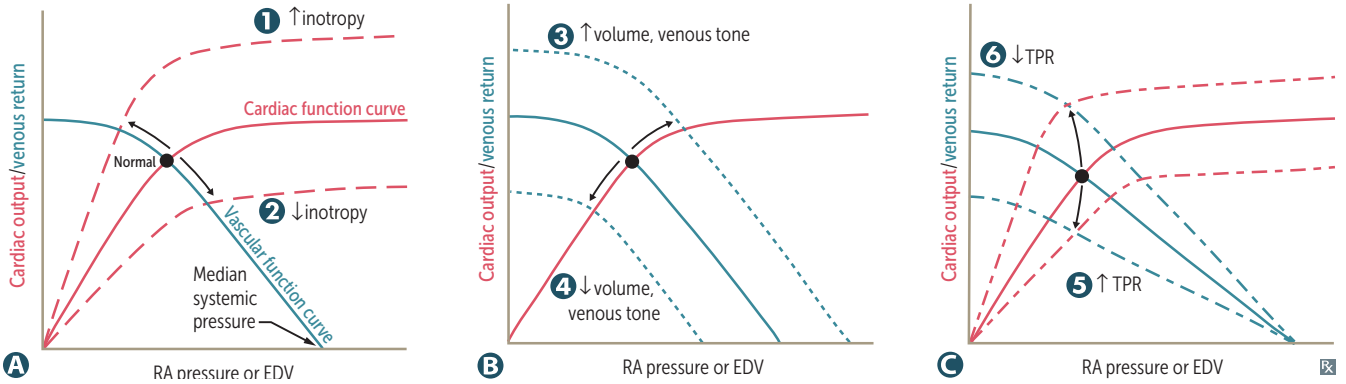


FIGURE 1-26. Effect of increased contractility, afterload, and preload on the pressure-volume loop. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SV, stroke volume.



Intersection of curves = operating point of heart (ie, venous return and CO are equal).

GRAPH	EXAMPLES
A Inotropy	1 Catecholamines, digoxin ⊕ 2 Uncompensated HF, narcotic overdose, sympathetic inhibition ⊖
B Venous return	3 Fluid infusion, sympathetic activity ⊕ 4 Acute hemorrhage, spinal anesthesia ⊖
C Total peripheral resistance	5 Vasopressors ⊕ 6 Exercise, AV shunt ⊖

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).

FIGURE 1-27. Cardiac (red) and vascular (blue) function curves. Changes in inotropy, venous return, and total peripheral resistance often occur in tandem. CO, cardiac output; EDV, end-diastolic volume; HF, heart failure; RA, right atrium; SVR, systemic vascular resistance.

- **Cardiac function curve:** How does preload (RA pressure or EDV) affect CO? This should sound familiar; it is the Frank-Starling relationship! As preload increases, up to a certain point, CO also increases.
- **Vascular function curve:** How does preload (RA pressure or EDV) affect venous return? Venous return is blood returning from systemic circulation to the right heart, and is influenced by RA pressure and preload (EDV). Venous return increases with decreasing RA pressure and EDV, because the pressure gradient from the systemic veins to the right atrium increases. The flat portion of the vascular curve corresponds to negative RA pressures. At negative pressures, veins collapse, preventing an increase in venous return to the heart (maximum venous return).

Figure 1-27 shows how several factors (eg, inotropic agents, changes in circulating volume, and changes in total peripheral resistance) alter the shape of the curves. Parameters that can be measured on the combined cardiac-vascular function curves include:

- **Steady-state CO and venous return:** Intersection of the cardiac and vascular function curves (panels A, B, and C) represents the new "steady-state" CO and venous return for a given set of parameters. Note in panel A, for example, how inotropic agents shift the cardiac function curve up or down (analogous to Figure 1-24), moving the point of intersection up or down, respectively. Increased contractility, for example, results in increased CO that shifts the cardiac function curve upward; vascular function curve does not change because venous return is not affected by changes in contractility. Note, however, that the new point of intersection is at a decreased RA pressure/EDV, which reflects the fact that ejection fraction increases (ie, more blood is ejected per beat) with increasing contractility.

- **Mean systemic pressure:** The pressure throughout the circulatory system if the heart stopped beating (ie, venous pressure = arterial pressure). If systemic pressure is equal everywhere, there is no gradient for any venous return to the heart, which corresponds to the **x-intercept of the vascular function curve** (= zero venous return). Increase in blood volume (eg, transfusion) or vasoconstriction (eg, sympathetic activation) results in an increase in the x-intercept/mean systemic pressure (Figure 1-27, panel B). Notably, the cardiac function curve is unchanged by change in blood volume, but the point of intersection is altered (often described as moving "up" or "down" the Frank-Starling curve with increasing or decreasing blood volume, respectively).
- **Systemic vascular resistance (SVR):** Changes in SVR affect both function curves (Figure 1-27, panel C). Increase in SVR secondary to arteriolar vasoconstriction (because arterioles are the major determinant of SVR) results in increased afterload that causes decreased CO (shifts cardiac function curve down). Increased SVR also results in less venous return for a given RA pressure due to vasoconstriction (rotates the vascular function curve counterclockwise). Note that the vascular function curve rotates up or down with changes in SVR, but the x-intercept is unchanged if mean systemic pressure is fixed.

CLINICAL CORRELATION

Venodilators (eg, nitroglycerin) increase the **compliance** of veins, allowing them to hold more blood. Thus, less blood will be stored in "stiffer" arteries → decrease in mean systemic pressure.

A summary of parameters that alter cardiac and vascular function curves is provided in Table 1-9.

THE CARDIAC CYCLE

The heart as a "pump" is more accurately described as two pumps in series (left and right sides of the heart). The right side (RA and RV) pumps deoxygenated blood into the lungs, and the left side (LA and LV) pumps oxygenated blood from the lungs to systemic circulation. The Frank-Starling principle ensures that the right and left "pumps" work in concert so that an increase in venous return leads to an increase in CO. For blood to move simultaneously and efficiently through the right and left sides of the heart, it relies on coordinated electrical conduction pathways to ensure well-timed ventricular contraction bilaterally.

The Wiggers diagram (named after a cardiac physiologist) is used to illustrate valvular and electrical events in one full cardiac cycle with accompanying pressure and volume changes (Figure 1-28). For clarity, the Wiggers diagram is shown only for the left side of the heart (similar events are occurring on the right side of the heart at a lower pressure).

The Wiggers diagram is divided into seven phases (divided by vertical lines) that are best studied left to right with the valvular and electrical events that occur in each phase. Recall that PV loops divide the cardiac cycle into four phases: (1) isovolumetric contraction, (2) ventricular ejection, (3) isovolumetric relaxation, and (4) LV filling. The Wiggers diagram includes each of these phases, including subdivisions of some, accounting for the seven phases (labeled at the top of Figure 1-28).

TABLE 1-9. Parameters That Alter Cardiac and Vascular Function Curves

	POSITIVE INOTROPES	NEGATIVE INOTROPES	↑ BLOOD VOLUME	↓ BLOOD VOLUME	↑ SVR	↓ SVR
Cardiac Function Curve	↑ shift	↓ shift	No change	No change	↓ shift	↑ shift
Vascular Function Curve	No change	No change	↑ shift	↓ shift	Counterclockwise rotation	Clockwise rotation

SVR, systemic vascular resistance.

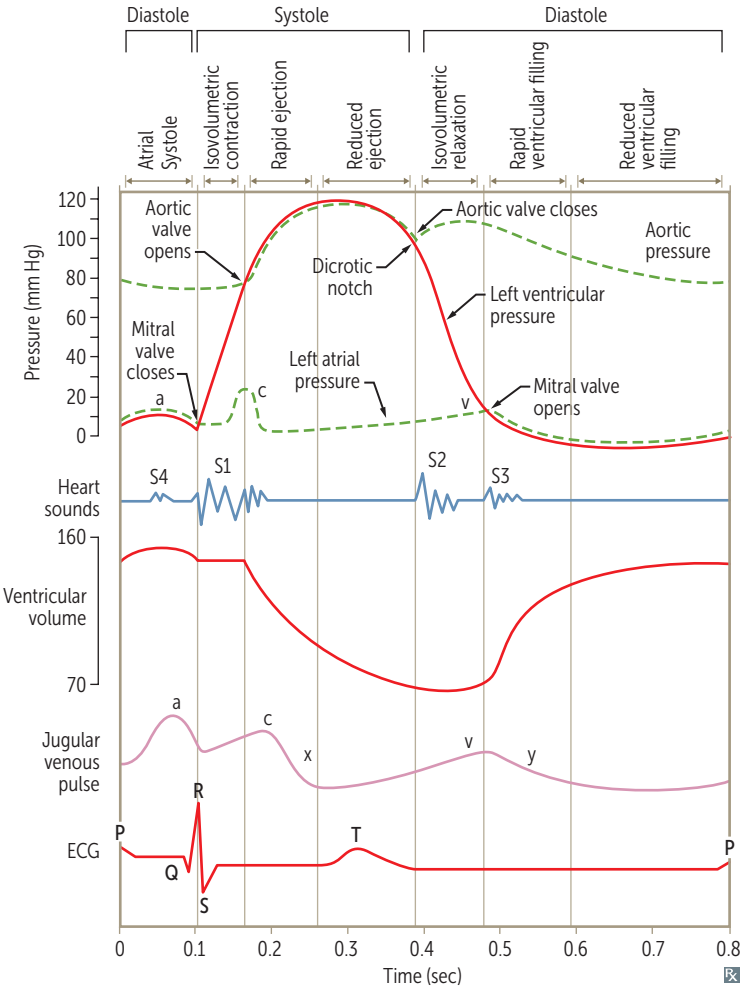


FIGURE 1-28. The Wiggers diagram. Mechanical and electrical events of a single cardiac cycle.

Pressure Tracings During the Cardiac Cycle

Pressure Changes in Diastole and Systole

Ventricular diastole begins with AoV closure (S_2) and lasts through the MV closure (S_1), whereas **ventricular systole** is defined as the part of the cardiac cycle from MV closure (S_1) to AoV closure (S_2) (Figure 1-28).

Pressure Changes in Left Ventricular Pressure, Aortic Pressure, and Jugular Venous Pressure

- **LV pressure:** The LV pressure curve is a function of changes in ventricular volume/pressure changes during diastole and systole.
  - Diastole: AoV closure marks the beginning of diastole. The LV relaxes and the pressure inside decreases. MV opens when LA pressure is higher than LV pressure. Blood enters the LV from the LA passively along a favorable pressure gradient. At the end of diastole, during atrial systole, the atrium contracts and actively fills the LV ("atrial kick"). When LV pressure exceeds LA pressure, the MV closes, marking the end of diastole and beginning of systole.
  - Systole: MV closure marks the beginning of systole. The LV contracts and LV pressure rapidly rises during isovolumetric contraction. When LV pressure is higher than aortic pressure, the AoV opens. As blood rushes out of the LV into the aorta, LV pressure drops. The AoV closes when aortic pressure exceeds LV pressure, marking the end of systole and beginning of diastole.

CLINICAL CORRELATION

Atrial fibrillation can cause loss of the "atrial kick" → decreased CO.

KEY FACT

- Heart valves OPEN when pressure upstream > pressure downstream.
- Heart valves CLOSE when pressure downstream > pressure upstream.