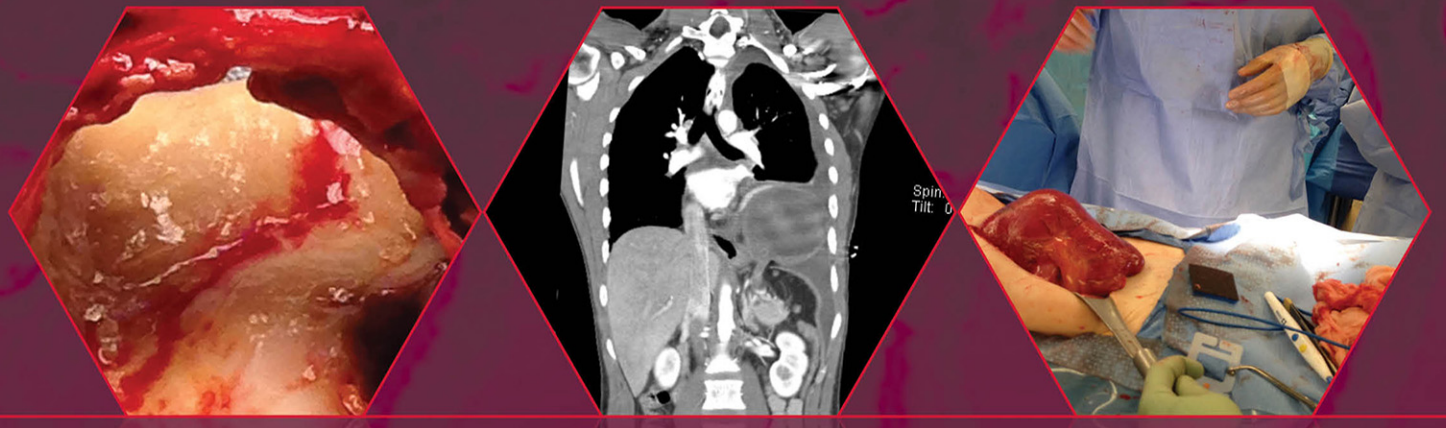
THIRD EDITION

FIRST AID FOR THE® BASIC SCIENCES

Organ Systems



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Mc Graw Hill Education

FIRST AID FOR THE® BASIC SCIENCES

Organ Systems

Third Edition

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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.

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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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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

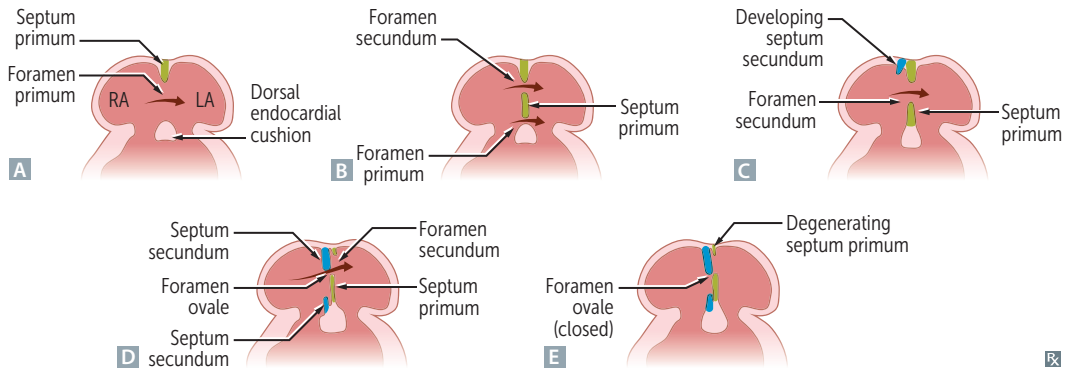

FIGURE 1-1. Embryologic development of the atrial septum.

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.

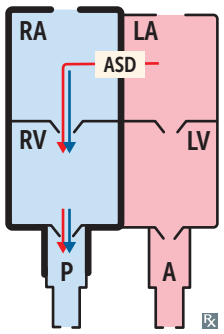

FIGURE 1-2. Atrial septal defect (ASD). In ASD, there is a left-to-right shunt between the atria. The right atrium (RA), right ventricle (RV), and pulmonary artery (P) become enlarged (indicated by bolded borders of heart chambers) owing to the influx of additional blood via the ASD left-to-right shunt.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

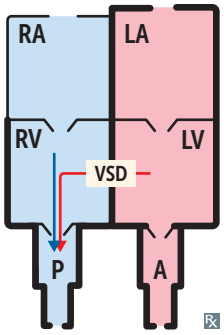

FIGURE 1-3. Ventricular septal defect (VSD). In VSD, there is a left-to-right shunt between the ventricles. The left atrium (LA) and left ventricle (LV) become enlarged (indicated by bolded borders of heart chambers) as a result of blood flow through this left-to-right shunt into the pulmonary artery 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.

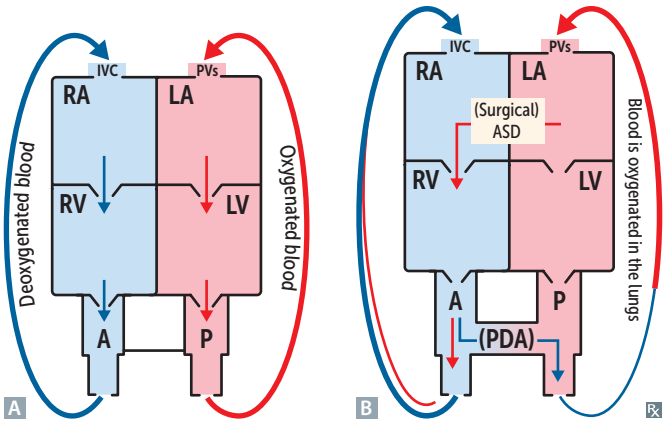

FIGURE 1-4. Transposition of the great vessels. Developmental defect in which the left ventricle connects to the pulmonary artery and the right ventricle connects to the aorta, resulting in two closed circuits. A Without a patent ductus arteriosus (PDA) and atrial septal defect (ASD), a closed circuit 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.

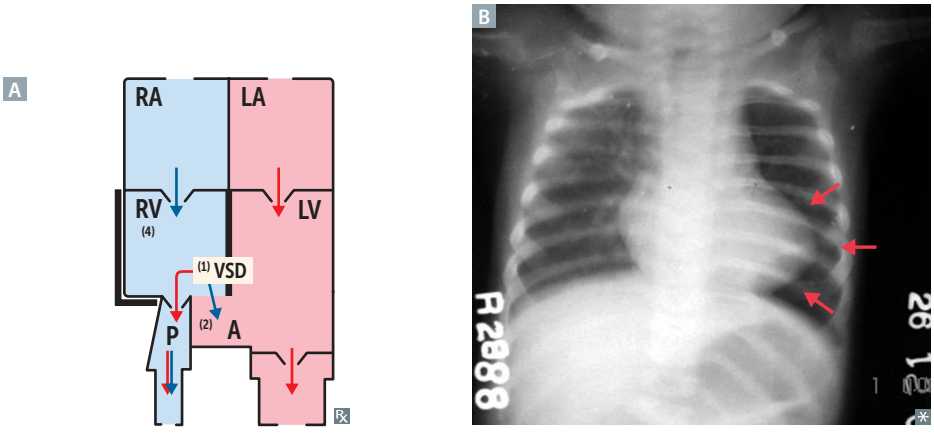

FIGURE 1-5. Tetralogy of Fallot. A Four concurrent defects: (1) Ventricular septal defect (VSD), (2) an overriding aorta, causing (3) right ventricular outflow obstruction (pulmonic stenosis) and subsequent (4) right ventricular hypertrophy. The extent of R-L shunting is determined by the degree of pulmonic 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.

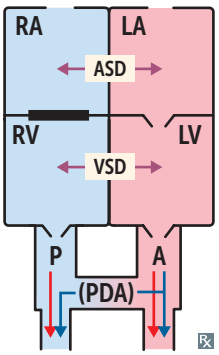

FIGURE 1-6. Tricuspid atresia. Failure of the tricuspid valve to develop, preventing blood from flowing from the right atrium (RA) into the right ventricle (RV). In order for oxygenated blood to reach the body, an atrial septal defect (ASD) and ventricular septal defect (VSD) must simultaneously be present 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.

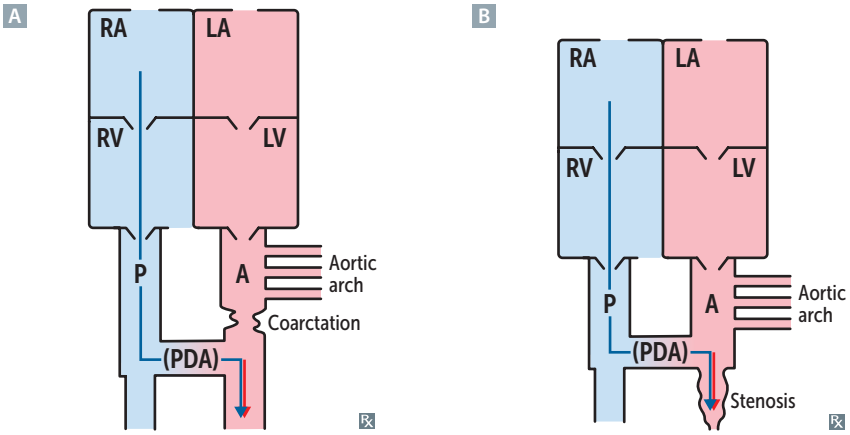

FIGURE 1-7. Preductal (infantile) and postductal (infantile) aortic coarctation. A Narrowing of the aorta proximal to the ductus arteriosus. This leads to decreased blood flow distal to the coarctation, and a right-to-left shunt if the patent ductus arteriosus (PDA) is kept open (can lead to cyanosis 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.

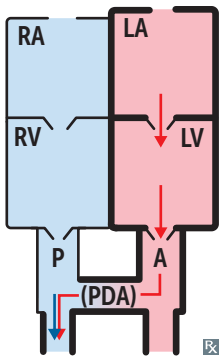

FIGURE 1-8. Patent ductus arteriosus (PDA). In PDA, a left-to-right shunt is present between the aorta (A) and pulmonary artery (P) due to the persistence of prostaglandins, a decrease of which normally triggers the closure of the PDA shortly after birth. A persistent PDA results in a continuous, machine-like 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).

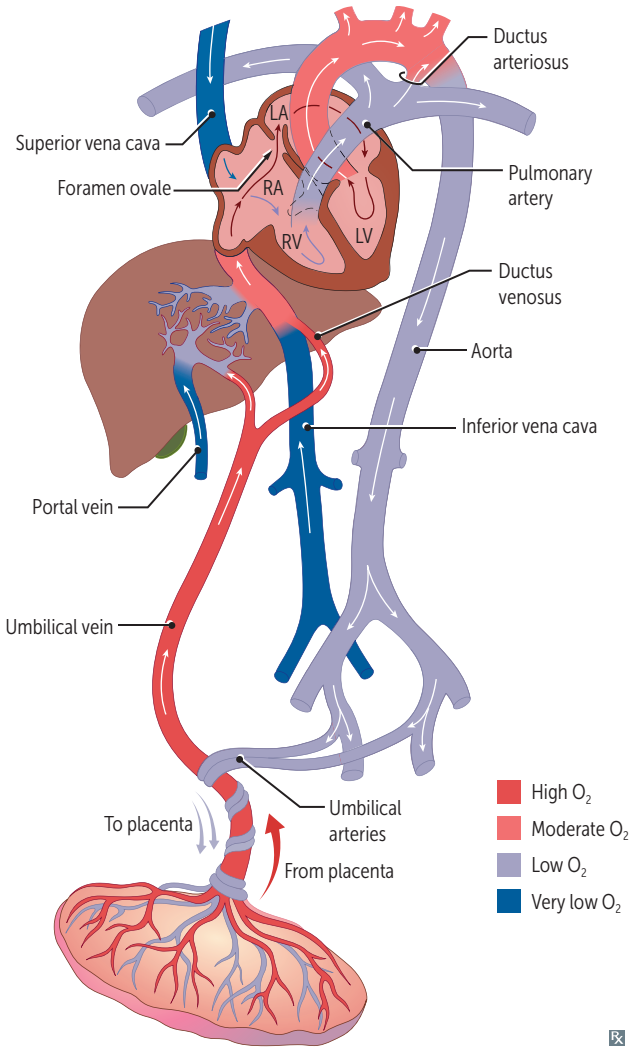

FIGURE 1-9. Fetal circulation. Most of the oxygenated blood reaching the heart via the umbilical vein (O_2 saturation ~ 80%) and inferior vena cava is diverted through the foramen ovale into the left atrium and pumped out into aortic arch vessels to the head, neck, and upper extremities (O_2 saturation ~ 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?

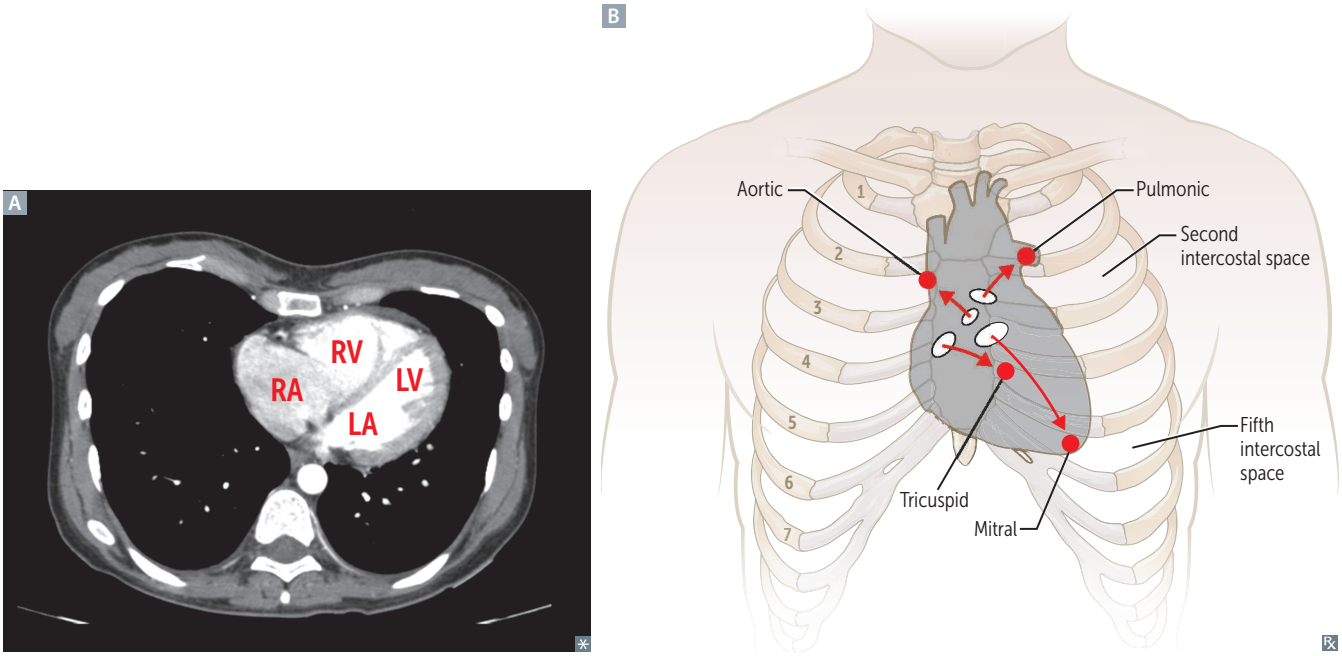

FIGURE 1-10. Anatomic relationships of the heart. A Axial CT of the heart. B Anatomic relationship of valves in the heart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

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.

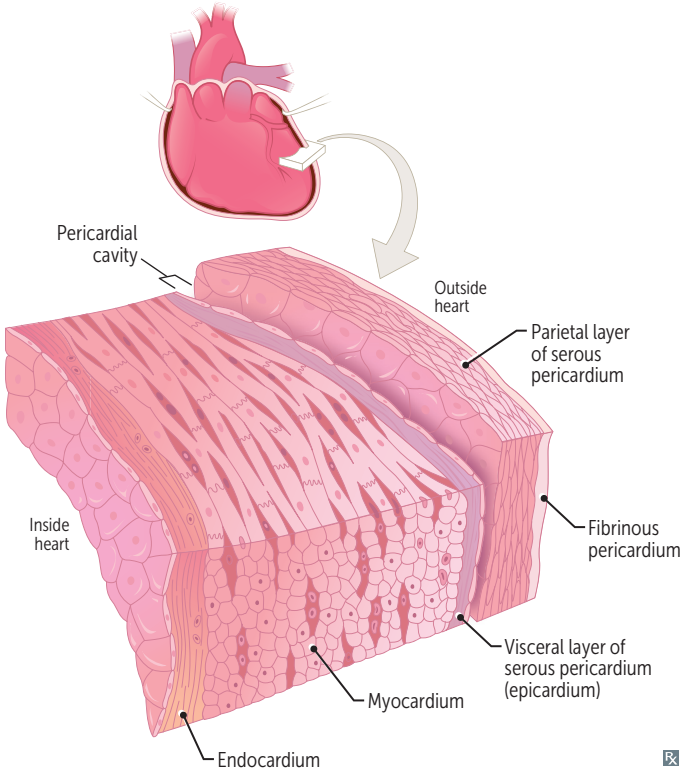

FIGURE 1-11. Layers of the heart. The three layers are epicardium, myocardium, and endocardium. The pericardial space is lined by a visceral and parietal layer of pericardium that encloses a thin layer of serous fluid.

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.

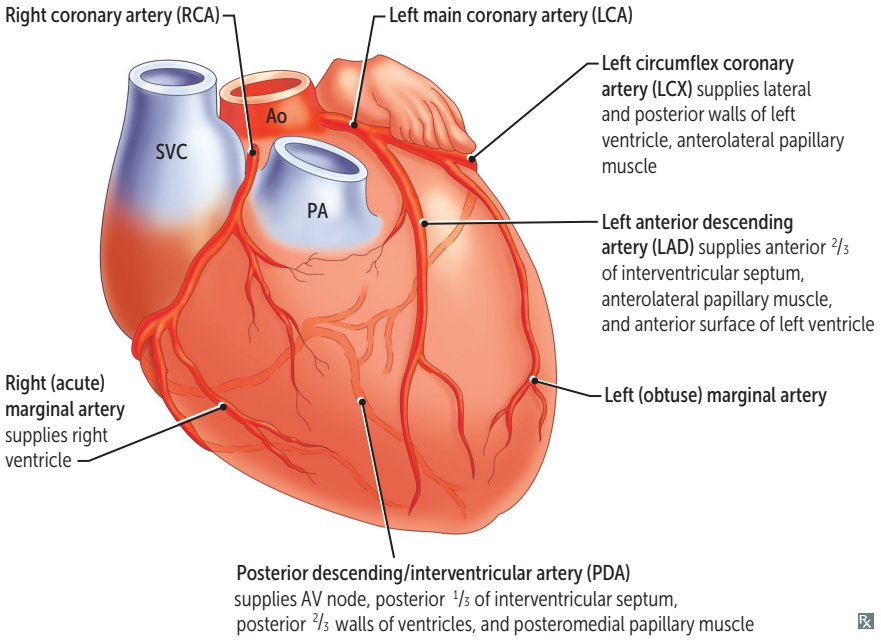

FIGURE 1-12. Coronary artery circulation. Ao, aorta; PA, pulmonary artery; SVC, superior vena cava.

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.**

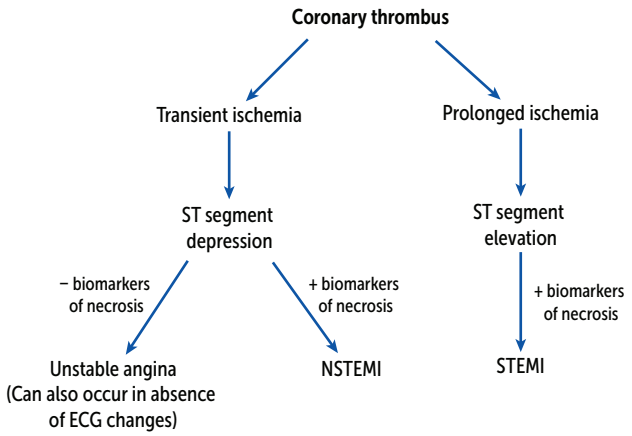

FIGURE 1-13. Spectrum of acute coronary syndrome. A coronary thrombus, depending on how occlusive it is and/or how much ischemia it causes, can lead to unstable angina, non-ST elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI), which are distinguished by ECG findings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

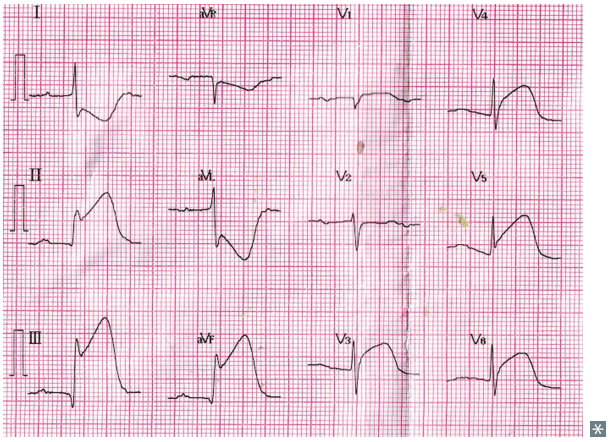

FIGURE 1-14. ECG findings in myocardial infarction. ST-segment elevation in the inferior (II, III, and aVF) and anterior (V_3–V_6) leads.

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.

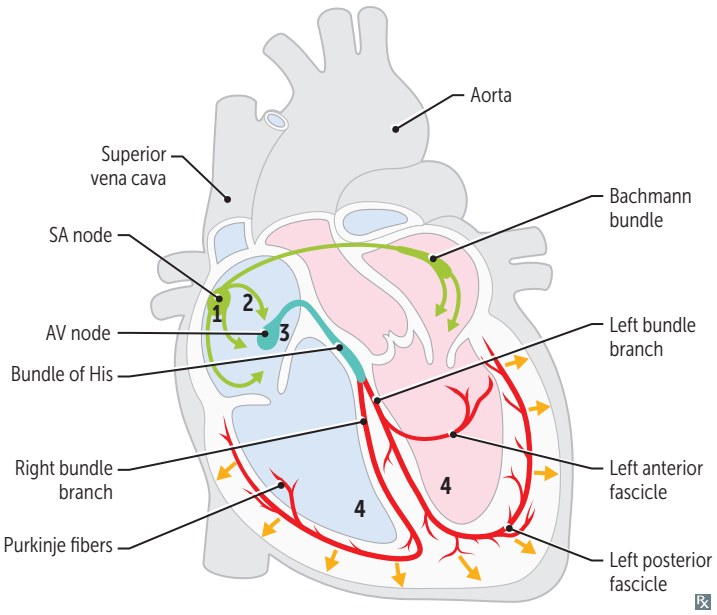

FIGURE 1-15. Anatomy of the conduction system in the heart.

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).