Congenital Heart Disease

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Chapter Outline

Congenital heart diseases are the most common form of birth defects and are the leading cause of death from birth abnormalities in the first year of life. These conditions affect approximately 8 of 1,000 live births, and an estimated 1 million people in the United States have congenital heart lesions. Some abnormalities are severe and require immediate medical attention, whereas many are less pronounced and have minimal clinical consequences. Although congenital heart defects are present at birth, milder defects may remain inapparent for weeks, months, or years and may even escape detection until adulthood.

The past half-century has witnessed tremendous advances in the understanding of the pathophysiology of congenital heart diseases and substantial improvements in the ability to evaluate and treat those afflicted. Research has shown that genetic mutations, environmental factors, maternal illness, or ingestion of toxins during pregnancy can contribute to cardiac malformations. However, specific etiologies remain unknown in most cases.

The survival of children with congenital heart disease has also improved dramatically in recent decades, largely because of better diagnostic and interventional techniques. However, the lifelong needs of affected patients include guidance regarding physical activity, pregnancy, and employment.

Formation of the cardiovascular system begins during the 3rd week of embryonic development. Soon after, a unique circulation develops that allows the fetus to mature in the uterus, using the placenta as the primary organ of gas, nutrient, and waste exchange. At birth, the fetal lungs inflate and become functional, making the placenta unnecessary and dramatically altering circulation patterns to allow the

neonate to adjust to life outside the womb. Given the remarkable complexity of these processes, it is easy to envision ways that cardiovascular malfunctions could develop.

This chapter begins with an overview of fetal cardiovascular development and then describes the most common forms of congenital heart disease.

NORMAL DEVELOPMENT OF THE CARDIOVASCULAR SYSTEM

By the 3rd week of gestation, the nutrient and gas exchange needs of the rapidly growing embryo can no longer be met by diffusion alone, and the tissues begin to rely on the developing cardiovascular system to deliver these substances over long distances.

Development of the Heart Tube

In the middle of the 3rd week of embryogenesis, mesodermal cells proliferate at the cranial end of the early embryonic disc. They eventually form two longitudinal cell clusters known as angioblastic cords. These cords canalize and become paired endothelial heart tubes (Fig. 16-1). Lateral embryonic folding gradually causes these two tubes to oppose one another and allows them to fuse in the ventral midline, forming a single endocardial tube by day 22. From inside to outside, the layers of this primitive heart tube are an endothelial lining that becomes the endocardium, a layer of gelatinous connective tissue (cardiac jelly), and a thick muscular layer that is derived from the splanchnic mesoderm and develops into the myocardium. The endocardial tube is continuous with the aortic arch system rostrally and with the venous system caudally. The primitive heart begins to beat around day 22 or 23, causing blood to circulate by the beginning of the 4th week. The space overlying the developing cardiac area eventually becomes the pericardial cavity, housing the future heart.

Formation of the Heart Loop

As the tubular heart grows and elongates, it develops a series of alternate constrictions and dilations, creating the first sign of the primitive heart chambers—the truncus arteriosus, the bulbus cordis, the primitive ventricle, the primitive atrium,

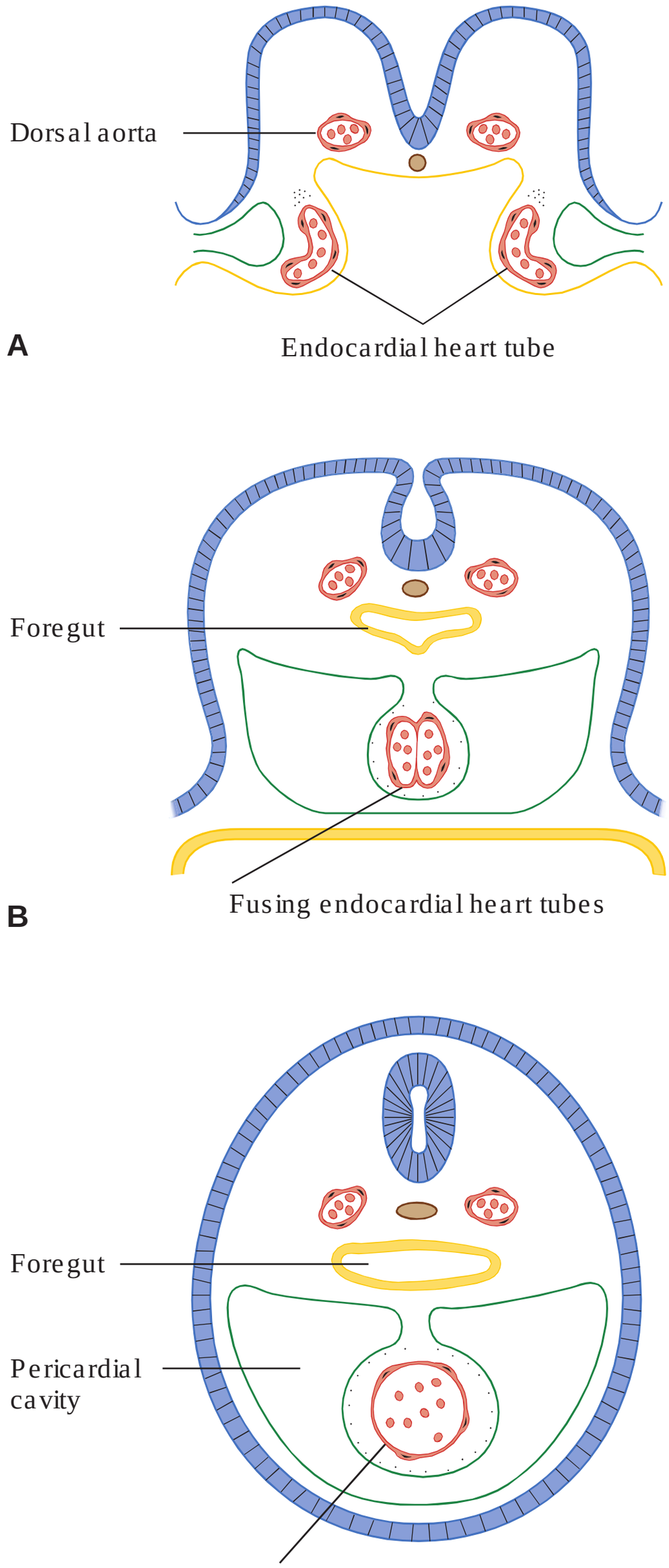

FIGURE 16-1. Embryonic transverse sections illustrating fusion of the two heart tubes into a single endocardial heart tube. A. 18 days. **B.** 21 days. **C.** 22 days.

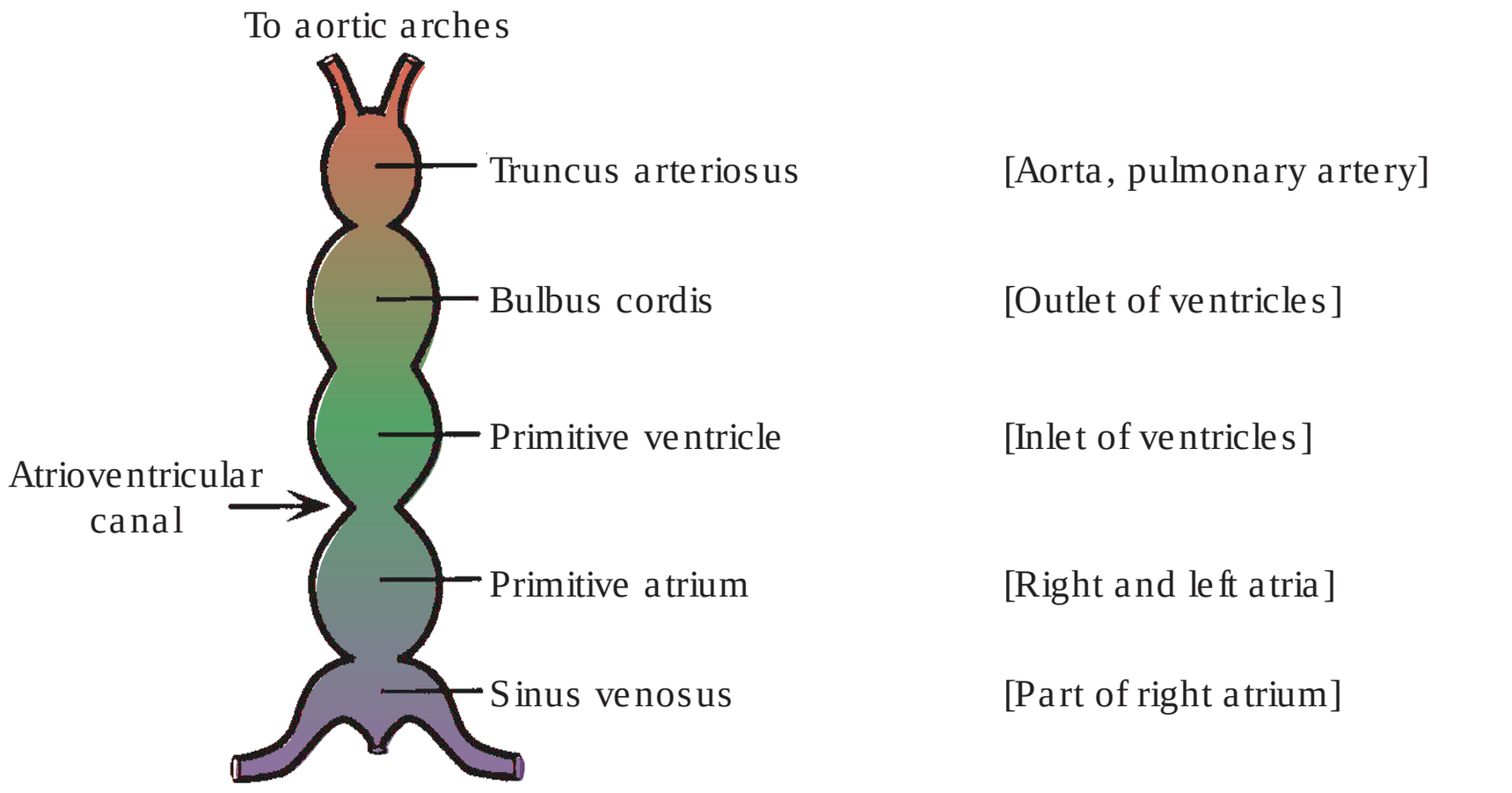

FIGURE 16-2. The straight heart tube at approximately 22 days. The structures that will ultimately form from each segment are listed in brackets.

and the sinus venosus (Fig. 16-2). Continued growth and elongation within the confined pericardial cavity force the heart tube to bend on itself on day 23, eventually forming a U-shaped loop with the round end pointing ventrally and to the right by day 28. The result of this looping is placement of the atrium and sinus venosus above and behind the truncus arteriosus, bulbus cordis, and ventricle (Fig. 16-3). At this point, neither definitive septa between the developing chambers nor definitive valvular tissue have formed. The connection between the primitive atrium and ventricle is termed the **atrioventricular (AV) canal**. In time, the AV canal becomes two separate canals, one housing the tricuspid valve and the other the mitral valve. The sinus venosus is eventually incorporated into the right atrium, forming both the coronary sinus and a portion of the right atrial wall. The bulbus cordis and truncus arteriosus contribute to the future ventricular outflow tracts, forming parts of the proximal aorta and pulmonary artery.

Septation

Septation of the developing atrium, AV canal, and ventricle occurs between the 4th and 6th weeks. Although these events are described separately here, they actually occur simultaneously.

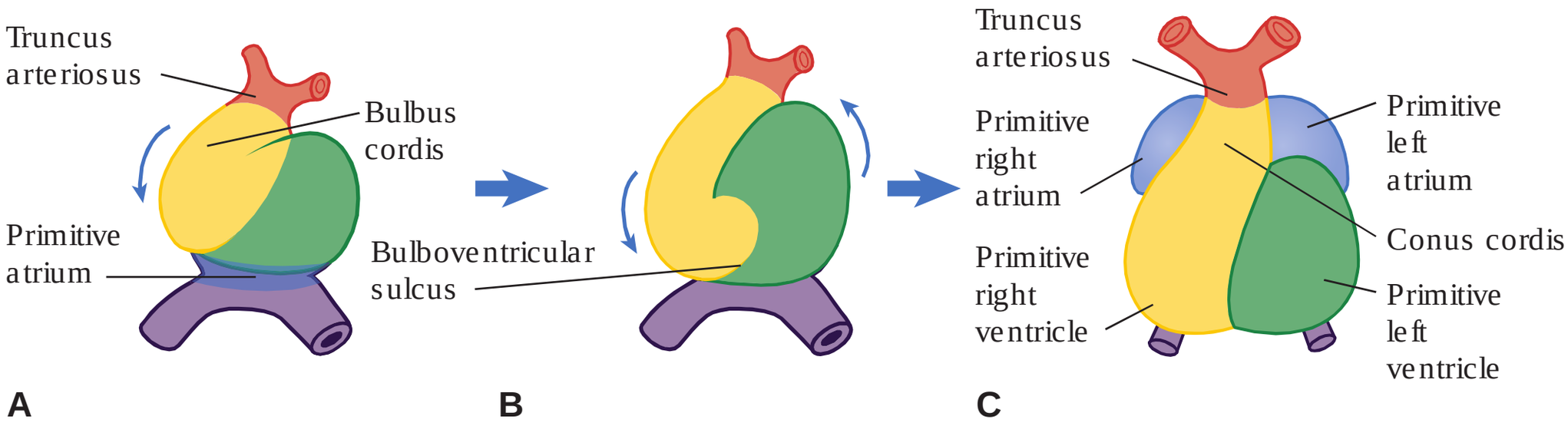

FIGURE 16-3. Formation of the heart loop. A,B. By day 23, continued growth and elongation within the confined pericardial space necessitate bending of the heart tube on itself, forming a U-shaped loop that points ventrally and to the right. **C.** Looping eventually places the atria above and behind the primitive ventricles.

Septation of the Atria

The primary atrial septum, also known as the **septum primum**, begins as a ridge of tissue on the roof of the common atrium that grows downward into the atrial cavity (Fig. 16-4). As the septum primum advances, it leaves a large opening known as the **ostium primum** between the crescent-shaped leading edge of the septum and the endocardial cushions surrounding the AV canal. The ostium primum allows passage of blood between the forming atria. Eventually, the septum primum fuses with the superior aspect of the endocardial cushions (described in more detail in the next section), obliterating the ostium primum. However, before closure of the ostium primum is complete, small perforations appear in the center of the septum primum that ultimately coalesce to form the **ostium secundum**, preserving a pathway for blood flow between the atria (see Fig. 16-4). Following closure of the ostium primum, a second, more muscular membrane, the **septum secundum**, begins to develop immediately to the right of the superior aspect of the septum primum. This septum grows downward and overlaps the ostium secundum. The septum secundum eventually fuses with the endocardial cushions, although only in a partial fashion, leaving an oval-shaped opening known as the **foramen ovale**. The superior edge of the septum primum then gradually regresses, leaving the lower edge to act as a "flap-like" valve that allows only right-to-left flow through the foramen ovale (Fig. 16-5). During gestation, blood passes from the right atrium to the left atrium because the pressure in the fetal right atrium is greater than that in the left atrium. This pressure gradient changes direction postnatally, causing the valve to close, as described later.

Septation of the Atrioventricular Canal

Growth of the **endocardial cushions** contributes to atrial septation and, as described later, to the membranous portion of the interventricular septum. Endocardial cushions initially

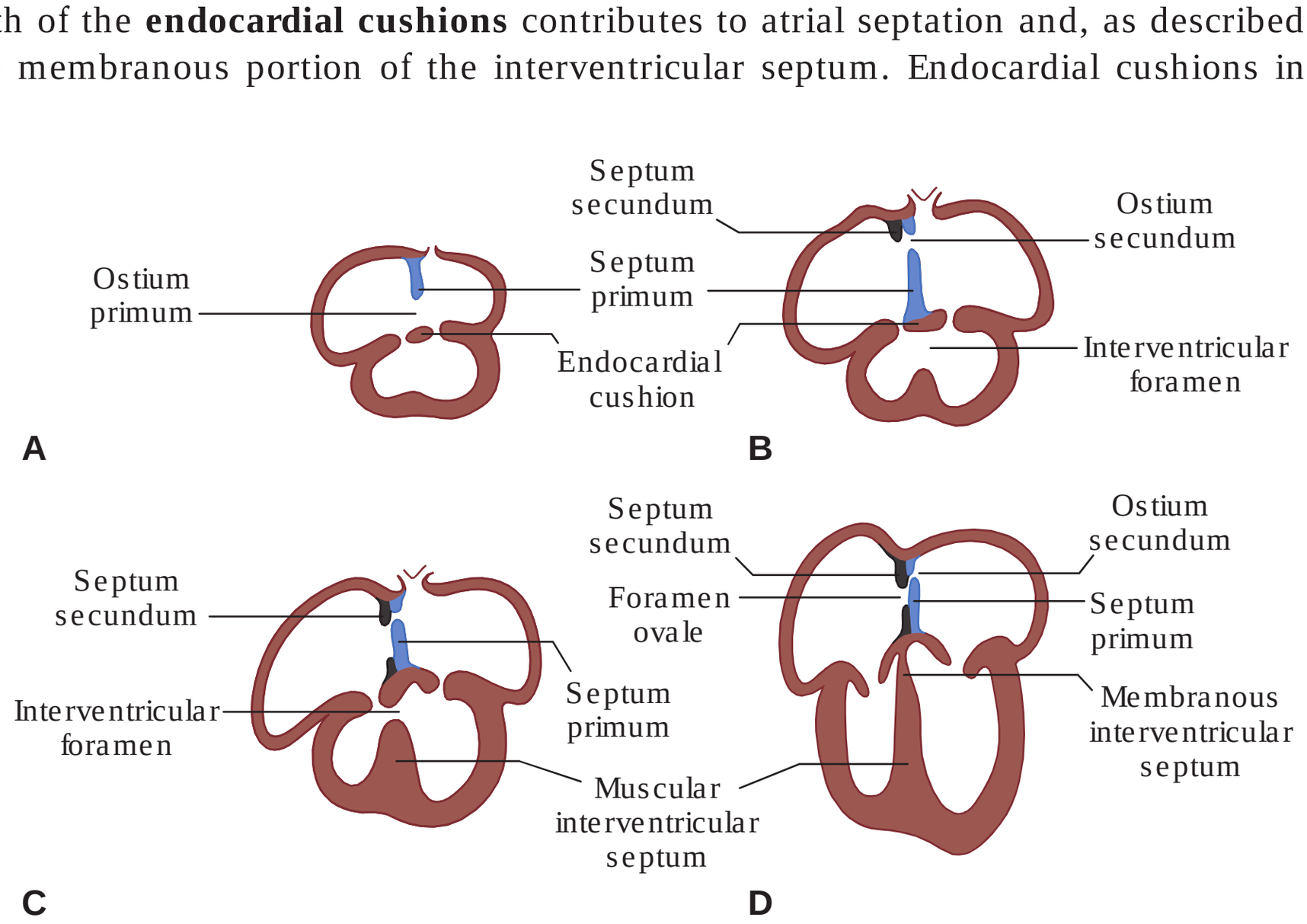

FIGURE 16-4. Atrial septal formation at 30 days (A), 33 days (B), and 37 days (C) of development as well as in the newborn (D). As the septum primum grows toward the ventricles, the opening between it and the AV canal is the ostium primum. Before the ostium primum completely closes, perforations within the upper portion of the septum primum form the ostium secundum. A second ridge of tissue, the septum secundum, grows downward to the right of the septum primum, partially covering the ostium secundum. The foramen ovale is an opening of the septum secundum that is covered by the "flap valve" of the lower septum primum. (Modified from Moss AJ, Adams FH. Heart Disease in Infants, Children, and Adolescents. Baltimore, MD: Williams & Wilkins; 1968:16.)

begin as swellings of the gelatinous connective tissue layer within the AV canal. They are then populated by migrating cells from the primitive endocardium and subsequently transform into mesenchymal tissue. Tissue growth occurs primarily in the horizontal plane, resulting in septation of the AV canal through the continued growth of the lateral, superior, and inferior endocardial cushions (Fig. 16-6). Septation creates the right and left canals that later give rise to the tricuspid and mitral orifices, respectively.

Septation of the Ventricles and Ventricular Outflow Tracts

At the end of the 4th week, the primitive ventricle begins to grow, leaving a median muscular ridge, the primitive interventricular septum. Most of the early increase in height of the septum results from dilation of the two new ventricles forming on either side of it. Only later does new cell growth in the septum itself contribute to its size. The free edge of the muscular interventricular septum does not fuse with the endocardial cushions; the opening that remains and allows communication between the right ventricle (RV) and left ventricle (LV) is the **interventricular foramen** (Fig. 16-7). This remains open until the end of the 7th week of gestation, when the fusion of tissue from the right and left bulbar ridges and the endocardial cushions forms the membranous portion of the interventricular septum.

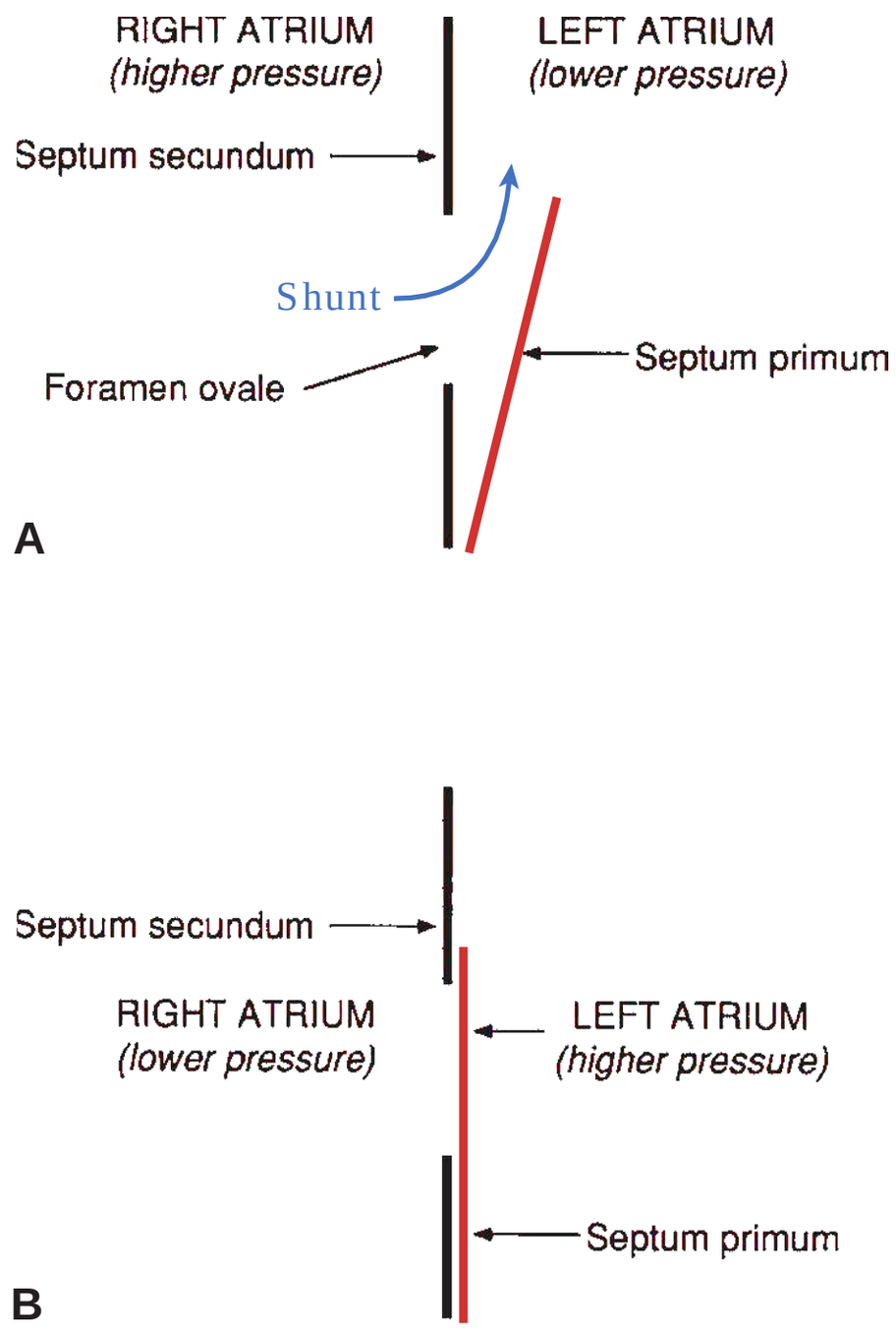

FIGURE 16-5. Diagrammatic depiction of the flap-type valve of the foramen ovale. A. Before birth, the valve permits only right-to-left flow of blood from the higher-pressured right atrium (RA) to the lower-pressured left atrium (LA). **B.** Following birth, the pressure in the LA becomes greater than that in the RA, causing the septum primum to close firmly against the septum secundum. (Derived from Moore KL, Persaud TVN. The Developing Human. Philadelphia, PA: WB Saunders; 1993:318.)

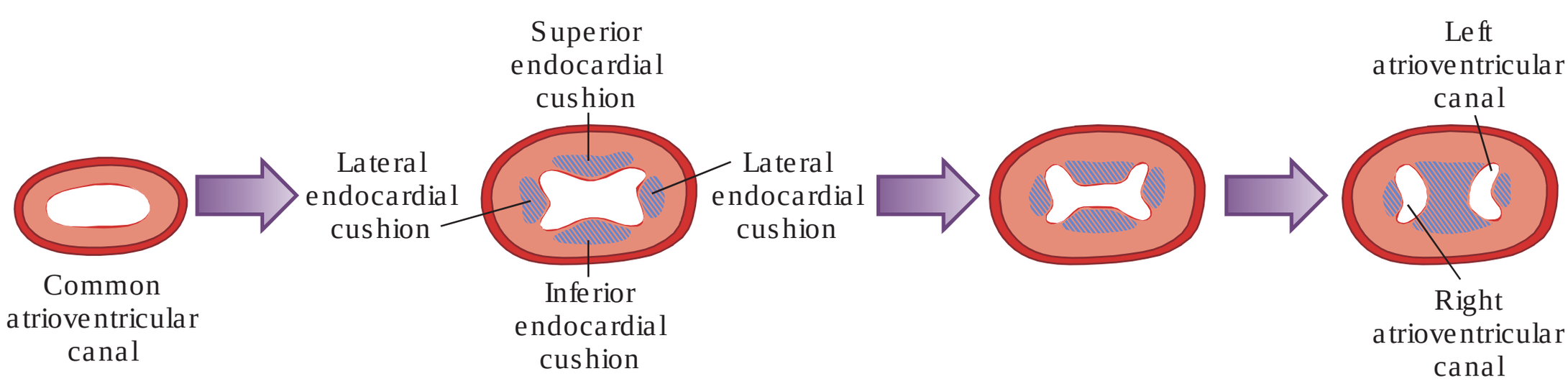

FIGURE 16-6. The progression of septal formation in the atrioventricular canal through successive stages. The septum forms through growth of the superior, inferior, and lateral endocardial cushions. The endocardial cushions are masses of mesenchymal tissue that surround the atrioventricular canal and aid in the formation of the orifices of the mitral and tricuspid valves, as well as the upper interventricular septum and lower interatrial septum.

During the 5th week, neural crest–derived mesenchymal proliferation occurring in the bulbus cordis and truncus arteriosus creates a pair of protrusions known as the bulbar ridges (Fig. 16-8). These ridges fuse in the midline and undergo a 180-degree spiraling process, forming the aorticopulmonary septum. This septum divides the bulbus cordis and the truncus arteriosus into two arterial channels, the pulmonary artery and the aorta, the former continuous with the RV and the latter with the LV.

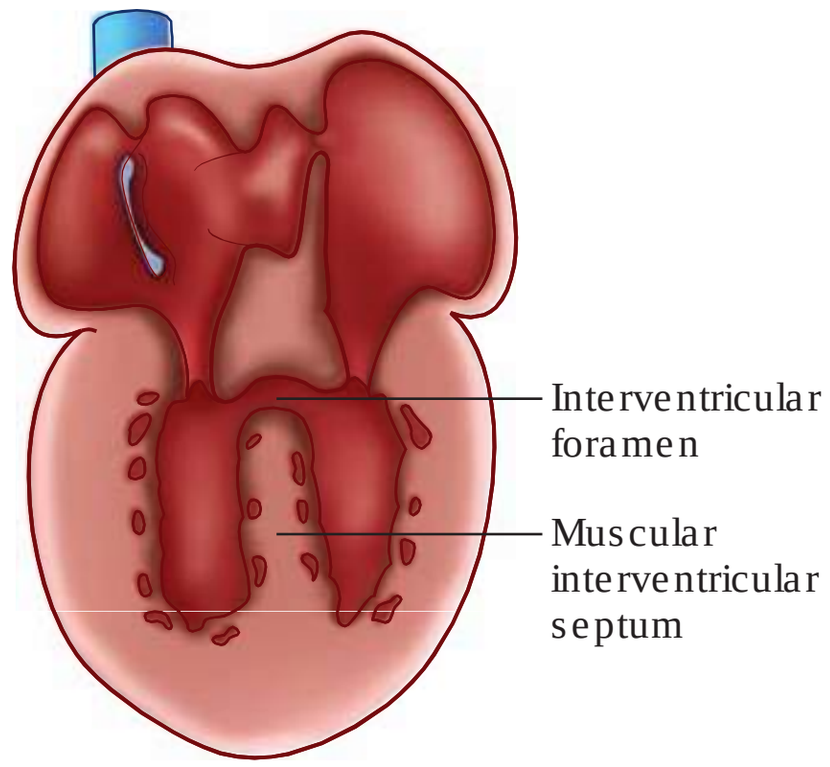

FIGURE 16-7. The interventricular septum and the interventricular foramen. (Derived from Moore KL, Persaud TVN. The Developing Human. Philadelphia, PA: WB Saunders; 1993:325.)

Development of the Cardiac Valves

Semilunar Valve Development (Aortic and Pulmonary Valves)

The semilunar valves start to develop just before the completion of the aorticopulmonary septum. The process begins when three outgrowths of subendocardial mesenchymal tissue form around both the aortic and pulmonary orifices. These growths are ultimately shaped and excavated by the joint action of programmed cell death and blood flow to create the three thin-walled cusps of both the aortic and pulmonary valves.

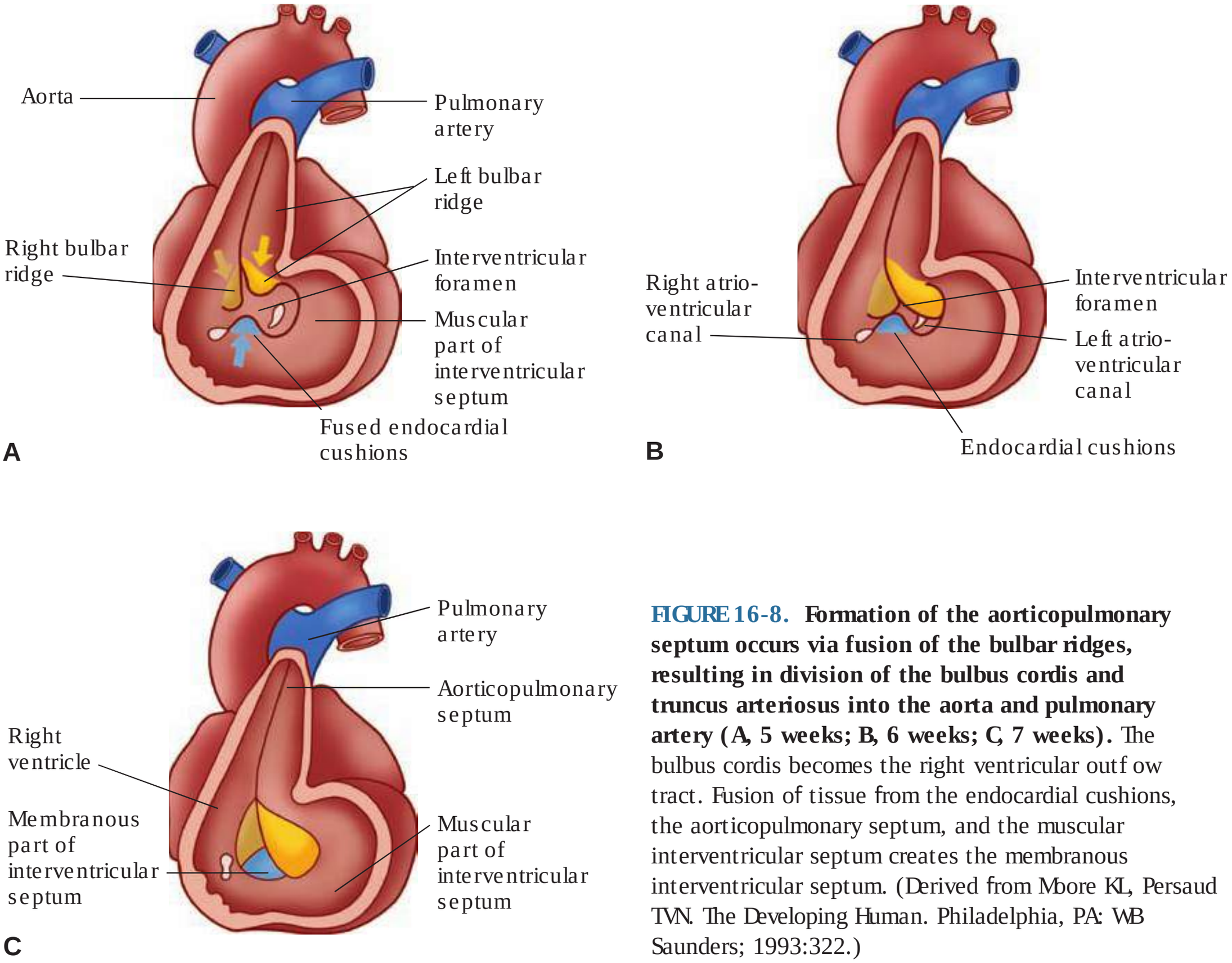

FIGURE 16-8. Formation of the aorticopulmonary septum occurs via fusion of the bulbar ridges, resulting in division of the bulbus cordis and truncus arteriosus into the aorta and pulmonary artery (A, 5 weeks; B, 6 weeks; C, 7 weeks). The bulbus cordis becomes the right ventricular outflow tract. Fusion of tissue from the endocardial cushions, the aorticopulmonary septum, and the muscular interventricular septum creates the membranous interventricular septum. (Derived from Moore KL, Persaud TVN. The Developing Human. Philadelphia, PA: WB Saunders; 1993:322.)

Atrioventricular Valve Development (Mitral and Tricuspid Valves)

After the endocardial cushions fuse to form the septa between the right and left AV canals, the surrounding subendocardial mesenchymal tissue proliferates and develops outgrowths similar to those of the semilunar valves. These are also sculpted by programmed cell death that occurs within the inferior surface of the nascent leaflets and in the ventricular wall. This process leaves behind only a few fine muscular strands to connect the valves to the ventricular wall (Fig. 16-9). The superior portions of these strands eventually degenerate and are replaced by strings of dense connective tissue, becoming the chordae tendineae.

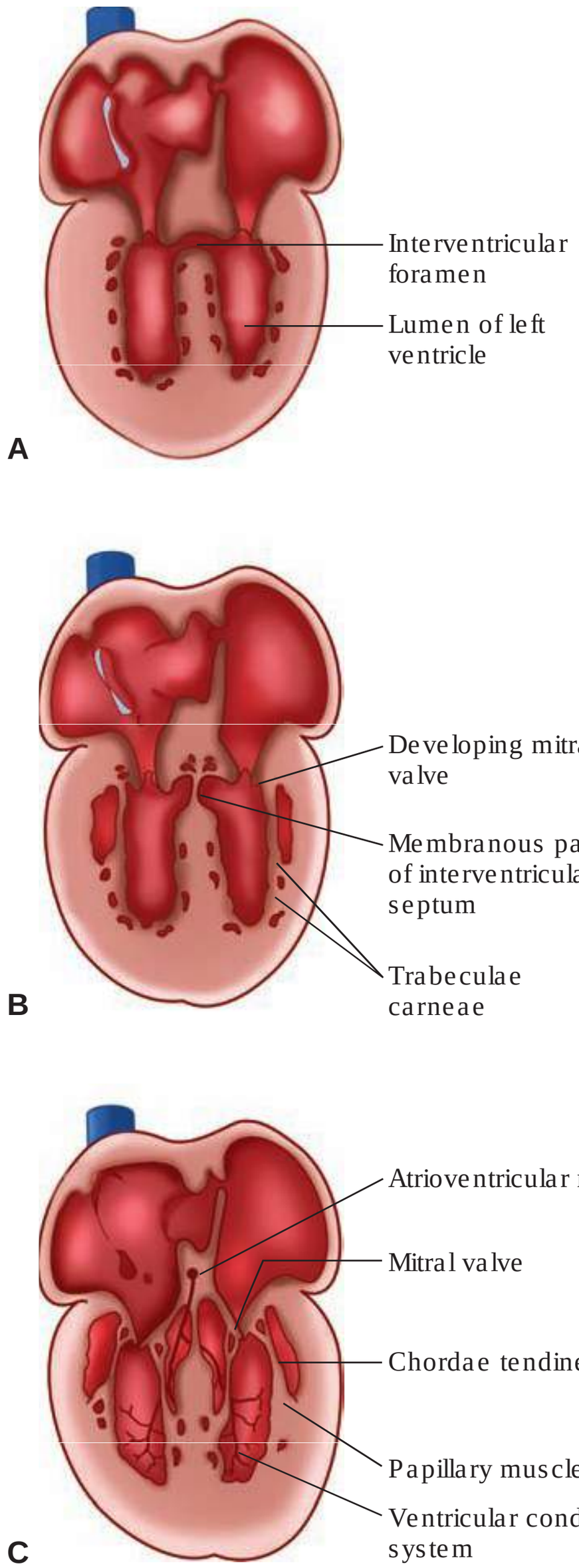

FIGURE 16-9. Proliferation of mesenchymal tissue surrounding the atrioventricular canals forms the atrioventricular valves. A–C. Progression of the process, including degeneration of myocardium and replacement by connective tissue that forms the chordae tendineae; their muscular attachments to the ventricular wall are the papillary muscles. (Derived from Moore KL, Persaud TVN. The Developing Human. Philadelphia, PA: WB Saunders; 1993:325.)

FETAL AND TRANSITIONAL CIRCULATIONS

The fetal circulation elegantly serves the needs of in utero development. At birth, the circulation automatically undergoes modifications that establish the normal blood flow pattern of a newborn infant.

Fetal Circulation

In fetal life, oxygenated blood leaves the placenta through the umbilical vein (Fig. 16-10). Approximately half of this blood is shunted through the fetal **ductus venosus**, bypassing the hepatic vasculature and proceeding directly into the inferior vena cava (IVC). The remaining blood passes through the portal vein to the liver and then into the IVC through the hepatic veins. IVC blood is therefore a mixture of well-oxygenated umbilical venous blood and the blood of low oxygen tension returning from the systemic veins of the fetus. Because of this mixture, the oxygen tension of inferior vena caval blood is higher than that of blood returning to the fetal right atrium from the superior vena cava. This distinction is important because these two streams of blood are partially separated within the right atrium to follow different circulatory paths. The consequence of this separation is that the fetal brain and myocardium receive blood of relatively higher oxygen content, whereas the more poorly oxygenated blood is diverted to the placenta (via the descending aorta and umbilical arteries) for subsequent oxygenation.

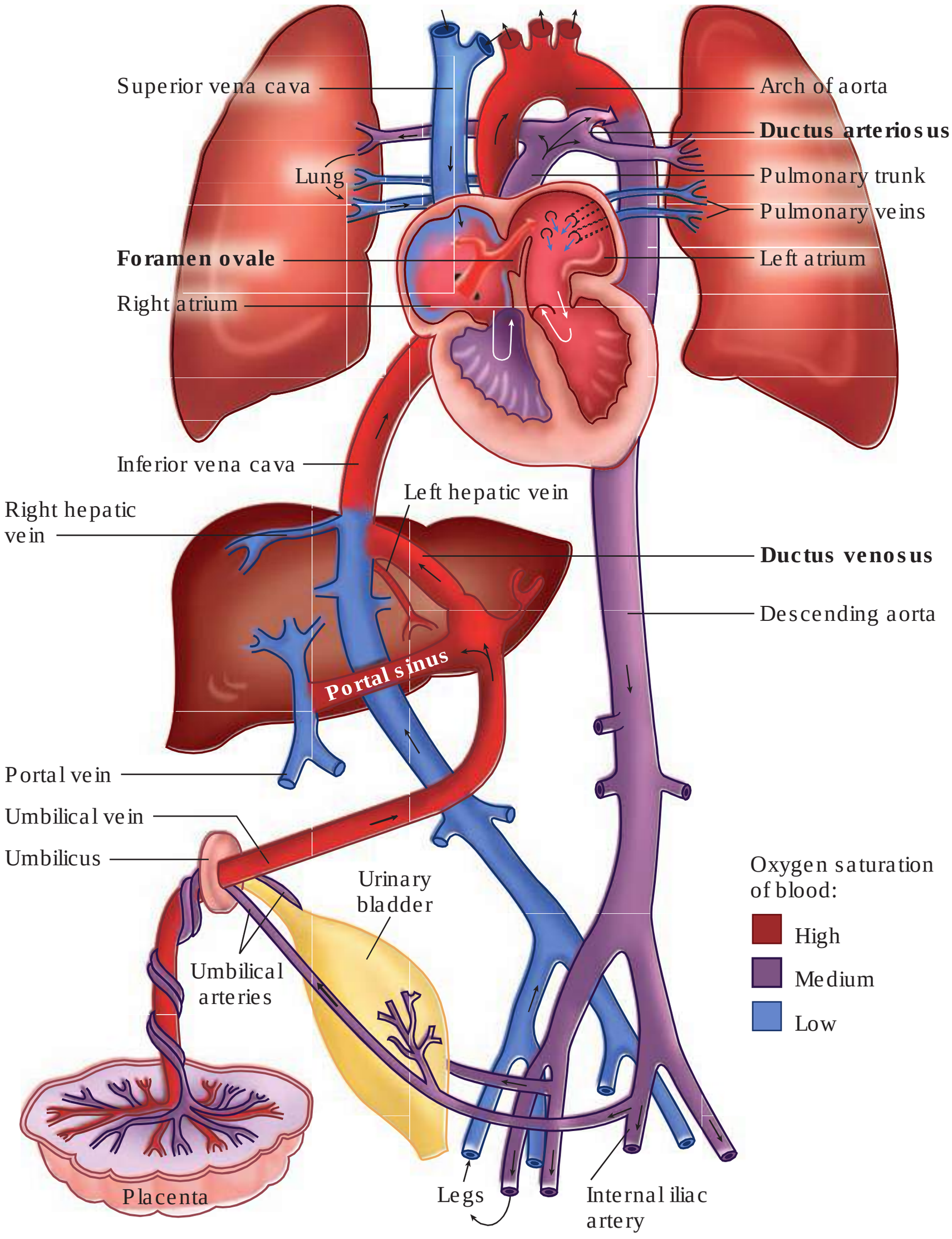

FIGURE 16-10. The fetal circulation. Arrows indicate the direction of blood flow. Three shunts (ductus venosus, foramen ovale, and ductus arteriosus) allow most of the blood to bypass the liver and lungs during fetal life but cease to function shortly after birth. (Modified from Moore KL, Persaud TVN. The Developing Human. Philadelphia, PA: WB Saunders; 1993:344.)

Most IVC blood entering the right atrium is directed to the left atrium through the foramen ovale. This intracardiac shunt of relatively well-oxygenated blood is facilitated by the inferior border of the septum secundum, termed the crista dividens, which is positioned such that it overrides the opening of the IVC into the right atrium. This shunted blood then mixes with the small amount of poorly oxygenated blood returning to the left atrium through the fetal pulmonary veins (remember that the lungs are not ventilated in utero; the developing pulmonary tissues actually remove oxygen from the blood). From the left atrium, blood flows into the LV and is then pumped into the ascending aorta. This well-oxygenated blood is distributed primarily to three territories: (1) approximately 9% enters

the coronary arteries and perfuses the myocardium, (2) 62% travels in the carotid and subclavian vessels to the upper body and brain, and (3) 29% passes into the descending aorta to the rest of the fetal body.

The remaining well-oxygenated inferior vena caval blood entering the right atrium mixes with poorly oxygenated blood from the superior vena cava and passes to the RV. In the fetus, the RV is the actual "workhorse" of the heart, providing two thirds of the total cardiac output. This output flows into the pulmonary artery and from there either into the lungs (12% of RV output), or through the **ductus arteriosus** into the descending aorta (88% of RV output), where it mixes with the better oxygenated blood from the LV described in the previous paragraph. This unequal distribution of right ventricular outflow is actually quite efficient. Bypassing the lungs is desired because the fetal lungs are filled with amniotic fluid and are incapable of gas exchange. The low oxygen tension of this fluid causes constriction of the pulmonary vessels, which increases pulmonary vascular resistance and facilitates shunting of blood through the ductus arteriosus to the systemic circulation. From the descending aorta, blood is distributed to the lower body and to the umbilical arteries, leading back to the placenta for gas exchange.

Transitional Circulation

Immediately following birth, the neonate rapidly adjusts to life outside the womb. The newly functioning lungs replace the placenta as the organ of gas exchange, and the three shunts (ductus venosus, foramen ovale, and ductus arteriosus) that operated during gestation ultimately close. This shift in the site of gas exchange and the resulting changes in cardiovascular architecture allow the newborn to survive independently.

As the umbilical cord is clamped or constricts naturally, the low-resistance placental flow is removed from the arterial system, resulting in an increase in systemic vascular resistance. Simultaneously, pulmonary vascular resistance falls for two reasons: (1) the mechanical inflation of the lungs after birth stretches the lung tissues, causing pulmonary artery expansion and wall thinning, and (2) vasodilatation of the pulmonary vasculature occurs in response to the rise in blood oxygen tension accompanying aeration of the lungs. This reduction in pulmonary resistance results in a dramatic rise in pulmonary blood flow. It is most marked within the first day after birth but continues for the next several weeks until adult levels of pulmonary resistance are achieved.

As pulmonary resistance falls and more blood travels to the lungs through the pulmonary artery, venous return from the pulmonary veins to the left atrium also increases, causing left atrial pressure to rise. At the same time, cessation of umbilical venous flow and constriction of the ductus venosus cause a fall in IVC and right atrial pressures. As a result, the left atrial pressure becomes greater than that in the right atrium, and the valve of the foramen ovale is forced against the septum secundum, eliminating the previous flow between the atria (see Fig. 16-5). Failure of the valve to permanently fuse to the septum secundum results in a patent foramen ovale (PFO), as described later in this chapter.

With oxygenation now occurring in the newborn lungs, the ductus arteriosus becomes superfluous and closes. During fetal life, a high circulating level of prostaglandin E_1 (PGE_1) is generated in response to relative hypoxia, which causes the smooth muscle of the ductus arteriosus to relax, keeping it patent. After birth, PGE_1 levels decline as the oxygen tension rises and the ductus therefore constricts. In a healthy full-term infant, this occurs during the first hours to days after delivery. The responsiveness of the ductus to vasoactive substances depends on the gestational age of the fetus, and it often fails to constrict in premature infants. This results in the congenital anomaly known as patent ductus arteriosus (PDA) (described below).

With the anatomic separation of the circulatory paths of the right and left sides of the heart now complete, the stroke volume of the LV increases and that of the RV decreases, equalizing

the cardiac output from both ventricles. The augmented pressure and volume load placed on the LV induces the myocardial cells of that chamber to hypertrophy, while the decreased pressure and volume loads on the RV result in gradual regression of RV wall thickness.

COMMON CONGENITAL HEART LESIONS

Congenital heart defects are generally well tolerated before birth. The fetus benefits from shunting of blood through the ductus arteriosus and the foramen ovale, allowing the bypass of most defects. It is only after birth, when the neonate has been separated from the maternal circulation and the oxygenation it provides, and the fetal shunts have closed, that congenital heart defects usually become manifest.

Congenital heart lesions can be categorized as cyanotic or acyanotic. Cyanosis refers to a blue-purple discoloration of the skin and mucous membranes caused by an elevated blood concentration of deoxygenated hemoglobin (usually >4 g/dL, which corresponds to an arterial O_2 saturation of approximately 80% to 85% in a neonate with a normal total hemoglobin level). In congenital heart disease, cyanosis results from defects that allow poorly oxygenated blood from the right side of the heart to be shunted to the left side, bypassing the lungs.

Acyanotic lesions include intracardiac or vascular stenoses, valvular regurgitation, and defects that result in left-to-right shunting of blood. Large left-to-right shunts at the atrial, ventricular, or great vessel level (all described in the following sections) cause the pulmonary artery volume and pressure to increase and can be associated with the later development of pulmonary arteriolar hypertrophy and subsequently increased resistance to flow. Over time, the elevated pulmonary resistance may force the direction of the original shunt to reverse, causing right-to-left flow to supervene, accompanied by the physical findings of hypoxemia and cyanosis. The development of pulmonary vascular disease as a result of a chronic large left-to-right shunt is known as Eisenmenger syndrome and is described later in the chapter.

Patients with congenital heart disease are susceptible to infective endocarditis. Chapter 8 describes the pathophysiology of endocarditis and summarizes the appropriate selection of patients for antibiotic prophylaxis prior to procedures that can result in bacteremia.

Acyanotic Lesions

Atrial Septal Defect

An atrial septal defect (ASD) is a persistent opening in the interatrial septum after birth that allows direct communication between the left and right atria. ASDs are relatively common, occurring with an incidence of 1 in 1,500 live births. They can occur anywhere along the atrial septum, but the most common site is at the region of the foramen ovale, termed an ostium secundum ASD (Fig. 16-11). This defect arises from inadequate formation of the septum secundum, excessive resorption of the septum primum, or a combination.

Less commonly, an ASD appears in the inferior portion of the interatrial septum, adjacent to the AV valves. Named as ostium primum defect, this abnormality results from the failure of the septum primum to fuse with the endocardial cushions.

A third type of atrial septal abnormality is termed a sinus venosus defect and is closely related to ASDs but is morphologically distinct. This condition represents an “unroofing” defect with absence of normal tissue between the right pulmonary vein(s) and the right atrium but is technically not a deficiency of the anatomic atrial septum (i.e., frequently the atrial septum itself is fully intact). As sinus venosus defects are often large and result in flow from the right pulmonary veins and left atrium into the right atrium, the pathophysiology is similar to that of a true ASD.

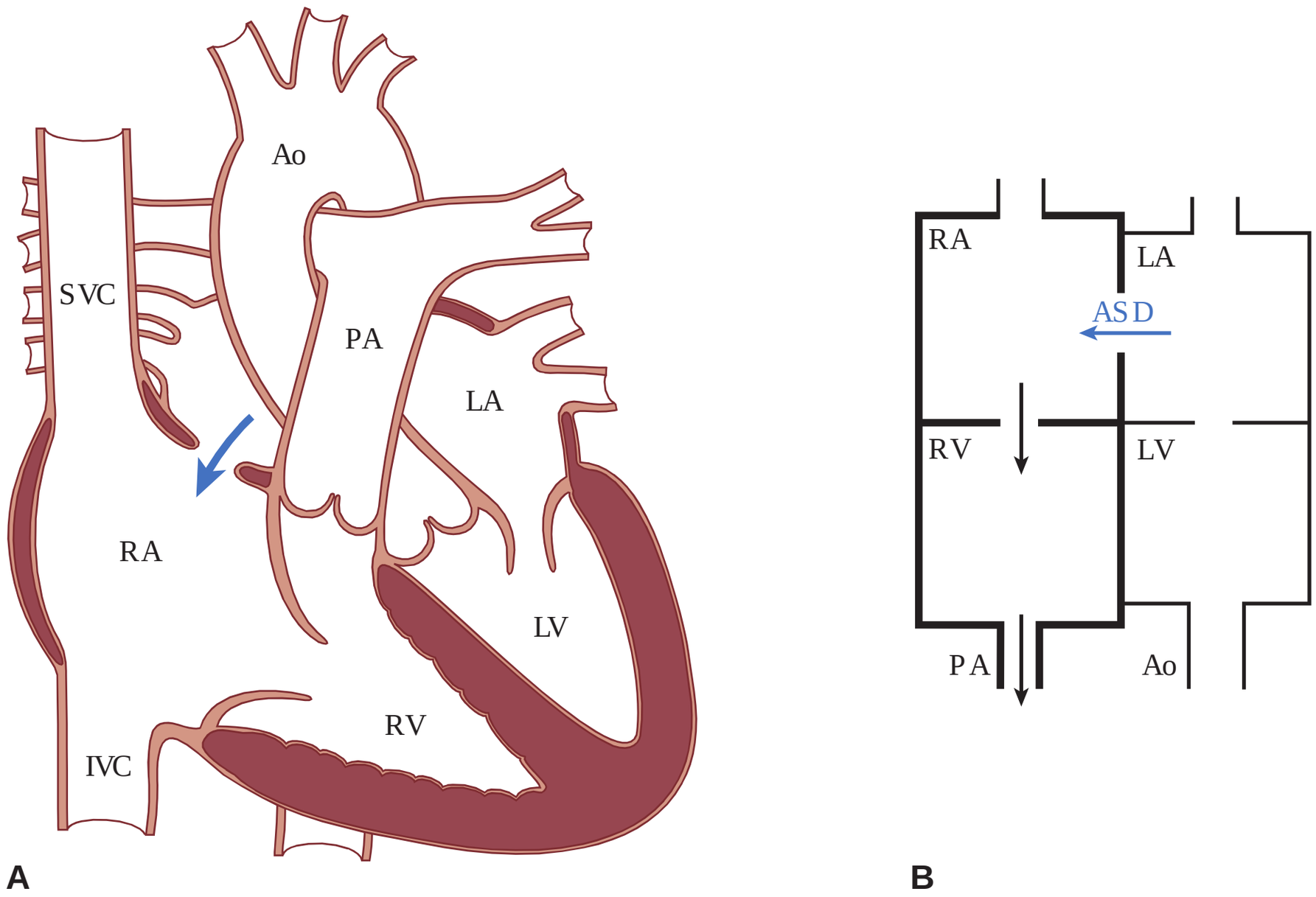

FIGURE 16-11. Atrial septal defect (ASD), ostium secundum type. A. The arrow indicates shunted flow from the left atrium (LA) into the right atrium (RA). **B.** Schematic representation of blood flow through an uncomplicated ASD, resulting in enlargement of the RA, right ventricle (RV), and pulmonary artery (PA). Ao, aorta; IVC, inferior vena cava; LV, left ventricle; SVC, superior vena cava.

Another distinct condition related to ASDs is patent foramen ovale, which is present in approximately 20% of the general population. It too is not a true ASD (i.e., no atrial septal tissue is "missing") but represents persistence of normal fetal anatomy. As described earlier, the foramen ovale typically functionally closes in the days after birth, and it is permanently sealed by the age of 6 months through fusion of the atrial septa. A PFO remains when this fusion fails to occur.

A PFO is usually clinically silent because the one-way valve, though not sealed, remains functionally closed since the left atrial pressure is higher than that in the right atrium. However, a PFO takes on significance if the right atrial pressure becomes elevated (e.g., in states of pulmonary hypertension or right-heart failure), resulting in pathologic right-to-left intracardiac shunting. In that case, deoxygenated blood passes directly into the arterial circulation. Occasionally, a PFO can be implicated in a patient who has suffered a systemic embolism (e.g., a stroke). This situation, termed paradoxical embolism, occurs when thrombus in a systemic vein breaks loose, travels to the right atrium, then passes across the PFO to the left atrium if right-heart pressures are elevated, at least transiently (e.g., during a cough, sneeze, or Valsalva type maneuver), and then into the systemic arterial circulation.

Pathophysiology

In the case of an uncomplicated ASD, oxygenated blood from the left atrium is shunted into the right atrium, but not vice versa. Flow through the defect is a function of its size and the filling properties (compliance) of the ventricles into which the atria pass their contents. Normally after birth, the RV becomes more compliant than does the LV, owing to the regression of right ventricular wall thickness and an increase in LV thickness, facilitating the left-to-right directed shunt at the atrial level. The result is volume overload and enlargement of the right atrium and RV (see Fig. 16-11B). If right ventricular compliance diminishes over time (because of the excessive load), the left-to-right shunt may lessen. Occasionally, if

severe pulmonary vascular disease develops (e.g., Eisenmenger syndrome), the direction of the shunt may actually reverse (causing right-to-left flow), such that desaturated blood enters the systemic circulation, resulting in hypoxemia and cyanosis.

Symptoms

Most infants with ASDs are asymptomatic. The condition may be detected by the presence of a murmur on routine physical examination during childhood or adolescence, but the exam findings are subtle and 25% of ASDs are not diagnosed until adulthood. If symptoms do occur, they include dyspnea on exertion, fatigue, and recurrent lower respiratory tract infections. The most common symptoms in adults are decreased stamina and palpitations due to atrial tachyarrhythmias resulting from right atrial enlargement.

Physical Examination

A prominent systolic impulse may be palpated along the lower-left sternal border, representing contraction of the dilated RV (termed an RV heave). The second heart sound (S_2) demonstrates a widened, fixed splitting pattern (see Chapter 2). This occurs because the normal respiratory variation in systemic venous return is countered by reciprocal changes in the volume of blood shunted across the ASD. In addition, the increased volume of blood flowing across the pulmonary valve often creates a systolic murmur at the upper-left sternal border. A mid-diastolic murmur may also be present at the lower-left sternal border owing to the increased flow across the tricuspid valve. Blood traversing the ASD itself does not produce a murmur because of the absence of a significant pressure gradient between the atria.

Diagnostic Studies

On chest radiograph, the heart is usually enlarged because of right atrial and right ventricular dilatation, and the pulmonary artery is prominent with increased pulmonary vascular markings. The electrocardiogram (ECG) shows right ventricular hypertrophy, often with right atrial enlargement and incomplete or complete right bundle branch block. In patients with the ostium primum type of ASD, left axis deviation is common and is thought to be a result of displacement and hypoplasia of the left bundle branch's anterior fascicle. Echocardiography demonstrates right atrial and right ventricular enlargement; the ASD may be visualized directly, or its presence may be implied by the demonstration of a transatrial shunt by Doppler flow assessment. The magnitude and direction of shunt flow and an estimation of right ventricular systolic pressure can also be determined by echo Doppler measurements.

Given the high sensitivity of echocardiography, it is rarely necessary to perform cardiac catheterization to confirm the presence of an ASD. However, catheterization may be useful to assess pulmonary vascular resistance and to diagnose concurrent coronary artery disease in older adults. In a normal person undergoing cardiac catheterization, the oxygen saturation measured in the right atrium is similar to that in the superior vena cava. However, an ASD with left-to-right shunting of well-oxygenated blood causes the saturation in the right atrium to be much greater than that of the superior vena cava.

Treatment

Most patients with ASDs remain asymptomatic. However, if the volume of shunted blood is hemodynamically significant (even in the absence of symptoms), elective surgical repair is recommended to prevent the development of heart failure or chronic pulmonary vascular disease. The defect is repaired by direct suture closure or with a pericardial or synthetic patch.

In children and young adults, morphologic changes in the right heart often return to normal after repair. Percutaneous ASD repair, using a closure device deployed via an intravenous catheter, is a less invasive alternative to surgery in selected patients with secundum ASDs.

Ventricular Septal Defect

A ventricular septal defect (VSD) is an abnormal opening in the interventricular septum (Fig. 16-12). VSDs are relatively common, having an incidence of 1.5 to 3.5 per 1,000 live births. They are most often located in the membranous (70%) and muscular (20%) portions of the septum. Rare VSDs occur just below the aortic valve or adjacent to the AV valves.

Pathophysiology

The hemodynamic changes and magnitude of the shunt that accompany VSDs depend on the size of the defect and the relative resistances of the pulmonary and systemic vasculatures. In small VSDs, the defect itself offers more resistance to flow than the pulmonary or systemic vasculature, thereby preventing a significant quantity of left-to-right shunting. Conversely, with larger "nonrestrictive" defects, the volume of the shunt is determined by the relative pulmonary and systemic vascular resistances. In the perinatal period, the pulmonary vascular resistance approximates the systemic vascular resistance, and minimal shunting occurs between the two ventricles. After birth, however, as the pulmonary vascular resistance falls, an increasing left-to-right shunt through the defect develops. When this shunt is large, the RV, pulmonary circulation, left atrium, and LV experience a relative volume overload. Initially, the increased blood return to the LV augments stroke volume (via the Frank–Starling mechanism); but over time, the increased volume load can result in progressive chamber dilatation, systolic dysfunction, and symptoms of heart failure. In addition, the augmented circulation

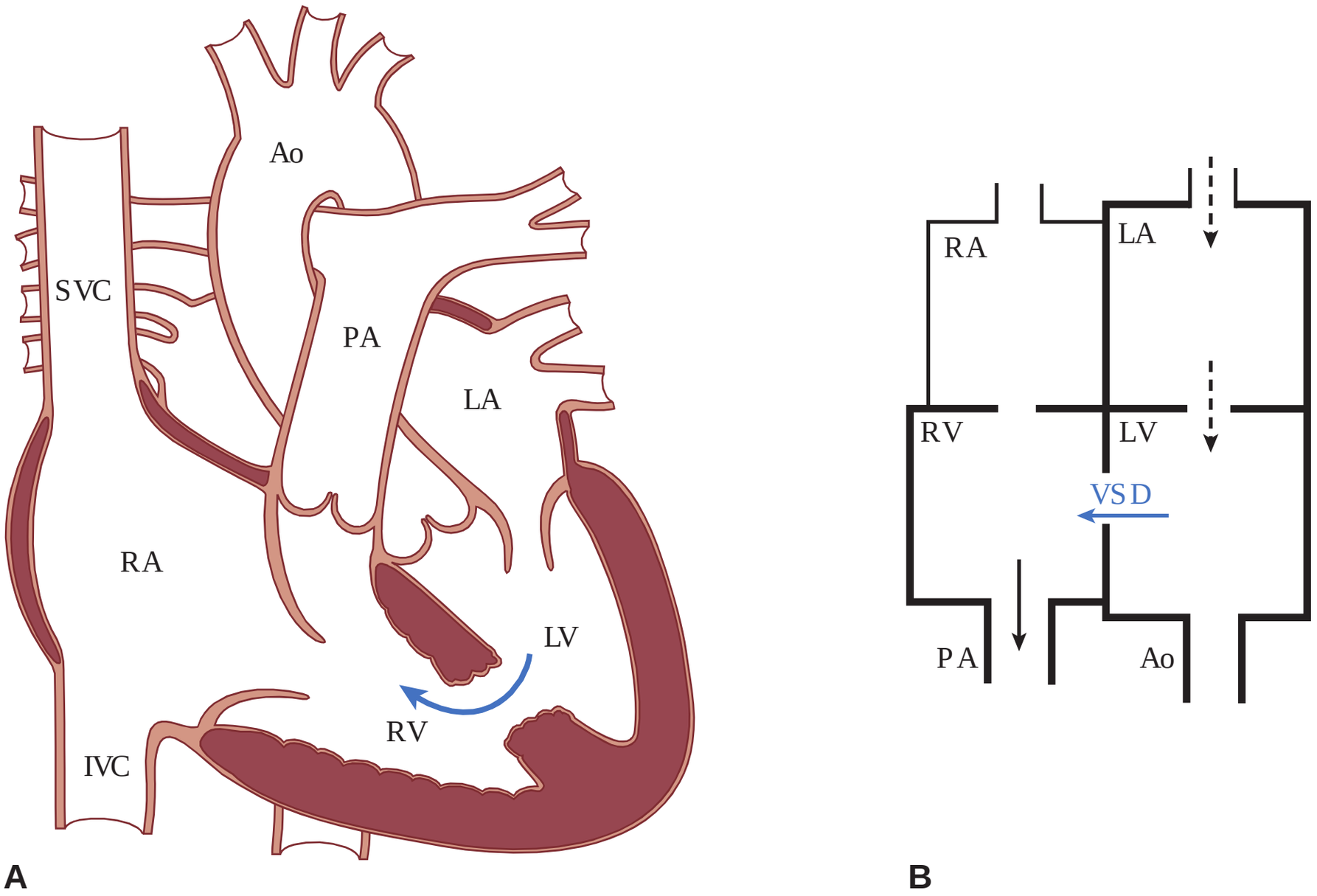

FIGURE 16-12. Ventricular septal defect (VSD). A. The arrow indicates shunted flow from the left ventricle (LV) toward the right ventricular (RV) outflow tract. **B.** Schematic representation of blood flow through an uncomplicated VSD. The dashed lines represent increased blood return to the left side of the heart as a result of the shunt, which causes enlargement primarily of the left atrium (LA) and LV. Ao, aorta; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; SVC, superior vena cava.

through the pulmonary vasculature can cause pulmonary vascular disease as early as 2 years of age. As pulmonary vascular resistance eventually approaches or exceeds systemic resistance, the intracardiac shunt may reverse its direction (i.e., Eisenmenger syndrome), leading to systemic hypoxemia and cyanosis.

Symptoms

Patients with small VSDs typically remain symptom free. Conversely, 10% of infants with VSDs have large defects and develop early symptoms of heart failure, including tachypnea, poor feeding, failure to thrive, and frequent lower respiratory tract infections. Patients with VSDs complicated by pulmonary vascular disease and reversed shunts may present with dyspnea and cyanosis. Bacterial endocarditis (see Chapter 8) can develop, regardless of the size of the VSD.

Physical Examination

The most common physical finding is a harsh holosystolic murmur that is best heard at the left sternal border. Smaller defects tend to have the loudest murmurs because of the great turbulence of flow that they cause. A systolic thrill can commonly be palpated over the region of the murmur. In addition, a mid-diastolic rumbling murmur can often be heard at the apex owing to the increased flow across the mitral valve. If pulmonary vascular disease develops, the holosystolic murmur diminishes as the pressure gradient across the defect decreases. In such patients, an RV heave, a loud pulmonic closure sound (P_2), and cyanosis may be evident.

Diagnostic Studies

On chest radiographs, the cardiac silhouette may be normal in patients with small defects, but in those with large shunts, cardiomegaly and prominent pulmonary vascular markings are present. If pulmonary vascular disease has developed, enlarged pulmonary arteries with peripheral tapering may be evident. The ECG shows left atrial enlargement and left ventricular hypertrophy in those with a large shunt, and right ventricular hypertrophy is usually evident if pulmonary vascular disease has developed. Echocardiography with Doppler studies can accurately determine the location of the VSD, identify the direction and magnitude of the shunt, and provide an estimate of right ventricular systolic pressure. Cardiac catheterization demonstrates increased oxygen saturation in the RV compared with the right atrium, the result of shunting of highly oxygenated blood from the LV into the RV.

Treatment

By age 2, at least 50% of small and moderate-sized VSDs undergo sufficient partial or complete spontaneous closure to make intervention unnecessary. Surgical correction of the defect is recommended in the first few months of life for children with accompanying heart failure or pulmonary vascular hypertension. Moderate-sized defects without pulmonary vascular disease but with significant left-to-right shunting can be corrected later in childhood. Less-invasive catheter-based treatments are also used in selected patients.

Patent Ductus Arteriosus

The ductus arteriosus is the vessel that connects the pulmonary artery to the descending aorta during fetal life. PDA results when the ductus fails to close after birth, resulting in a persistent connection between the great vessels (Fig. 16-13). It has an overall incidence of about 1 in 2,500 to 5,000 live term births. Risk factors for its presence include first trimester maternal rubella infection, prematurity, and birth at a high altitude.

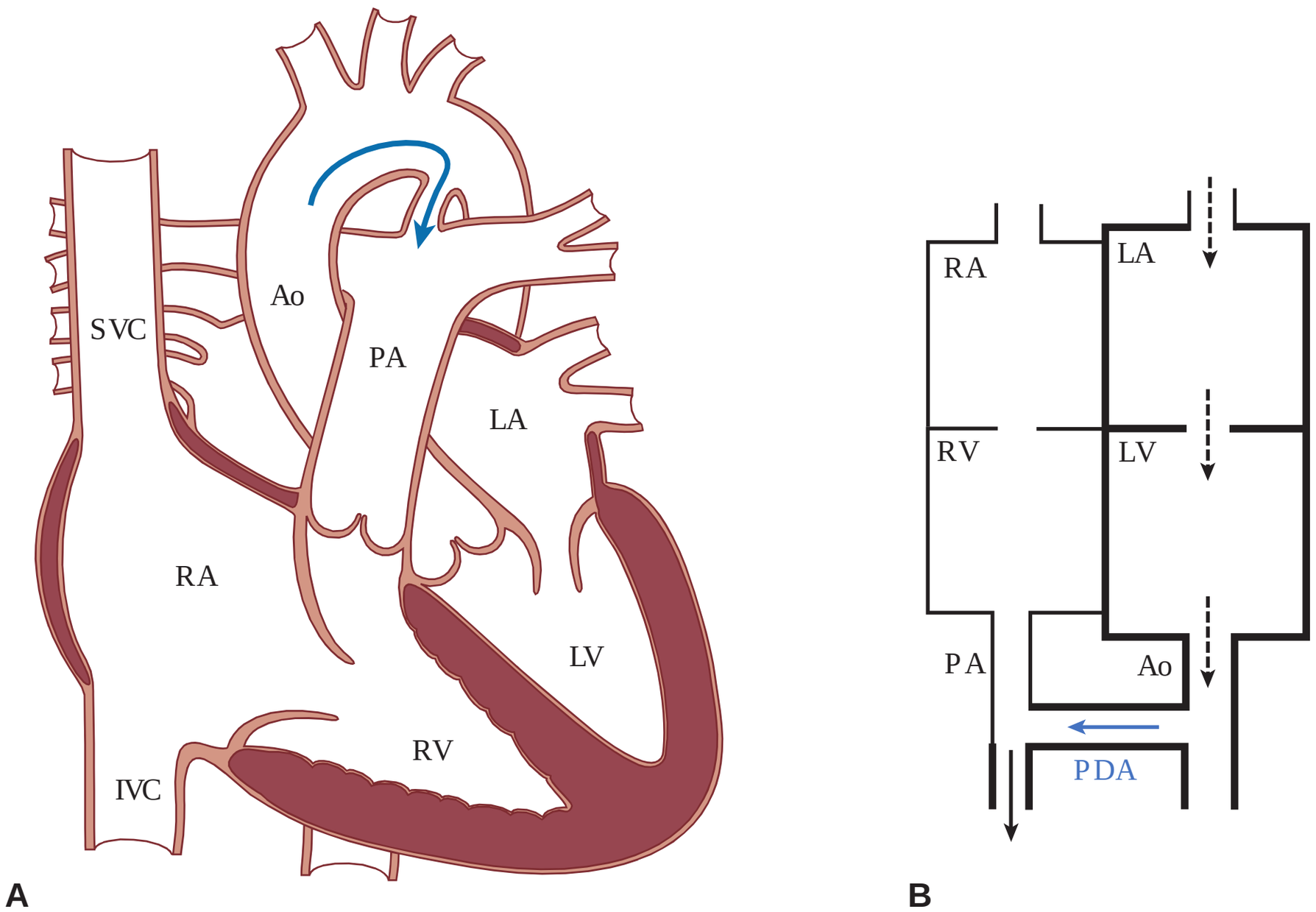

FIGURE 16-13. Patent ductus arteriosus (PDA). A. The arrow indicates shunted flow from the descending aorta (Ao) toward the pulmonary artery (PA). **B.** Schematic representation of blood flow through an uncomplicated PDA. The dashed lines represent increased blood return to the left side of the heart as a result of the shunt, which causes enlargement of the left atrium (LA), left ventricle (LV), and Ao. IVC, inferior vena cava; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Pathophysiology

As described earlier, the smooth muscle of the ductus arteriosus usually constricts after birth owing to the sudden rise in blood oxygen tension and a reduction in the level of circulating prostaglandins. Over the next several weeks, intimal proliferation and fibrosis result in permanent closure. Failure of the ductus to close results in a persistent shunt between the descending aorta and the left pulmonary artery. The magnitude of flow through the shunt depends on the cross-sectional area and length of the ductus itself as well as the relative resistances of the systemic and pulmonary vasculatures. Prenatally, when the pulmonary vascular resistance is high, blood is diverted away from the immature lungs to the aorta. As the pulmonary resistance drops postnatally, the shunt reverses direction, and blood flows from the aorta into the pulmonary circulation instead. Because of this left-to-right shunt, the pulmonary circulation, left atrium, and LV become volume overloaded. This can lead to left ventricular dilatation and left-sided heart failure, whereas the right heart remains normal unless pulmonary vascular disease ensues. If the latter does develop, Eisenmenger syndrome results, with reversal of the shunt causing blood to flow from the pulmonary artery, through the ductus, to the descending aorta. In this case, the resulting flow of desaturated blood to the lower extremities causes cyanosis of the feet; the upper extremities are not cyanotic, because they receive normally saturated blood from the aorta proximal to the ductus.

Symptoms

Children with small PDAs are generally asymptomatic. Those with large left-to-right shunts develop early congestive heart failure with tachycardia, poor feeding, slow growth, and recurrent lower respiratory tract infections. Moderate-sized lesions can present with fatigue, dyspnea, and palpitations in adolescence and adult life. Atrial fibrillation may occur owing to

left atrial dilatation. Turbulent blood flow across the defect can set the stage for endovascular infection, similar to endocarditis but more accurately termed endarteritis.

Physical Examination

The most common finding in a patient with a left-to-right shunt through a PDA is a continuous, machine-like murmur (see Fig. 2-10), heard best at the left subclavicular region. The murmur is present throughout the cardiac cycle because a pressure gradient exists between the aorta and pulmonary artery in both systole and diastole. However, if pulmonary vascular disease develops, the gradient between the aorta and the pulmonary artery decreases, leading to diminished flow through the PDA, and the murmur becomes shorter (the diastolic component may disappear). If Eisenmenger syndrome develops, lower extremity cyanosis and clubbing may be present as poorly oxygenated blood is shunted to the descending aorta.

Diagnostic Studies

With a large PDA, the chest radiograph shows an enlarged cardiac silhouette (left atrial and left ventricular enlargement) with prominent pulmonary vascular markings. In adults, calcification of the ductus may be visualized. The ECG shows left atrial enlargement and left ventricular hypertrophy when a large shunt is present. Echocardiography with Doppler imaging can visualize the defect, demonstrate flow through it, and estimate right-sided systolic pressures. Cardiac catheterization is usually unnecessary for diagnostic purposes. When performed in patients with a left-to-right shunt, it demonstrates a step up in oxygen saturation in the pulmonary artery compared with the RV, and angiography shows the abnormal flow of blood through the PDA.

Treatment

In the absence of other congenital cardiac abnormalities or severe pulmonary vascular disease, a PDA should generally be therapeutically occluded. Although many spontaneously close during the first months after birth, this rarely occurs later. Given the constant risk of endarteritis and the minimal complications of corrective procedures, even a small asymptomatic PDA is commonly referred for closure. For neonates and premature infants with congestive heart failure, a trial of prostaglandin synthesis inhibitors (e.g., indomethacin) can be administered in an attempt to constrict the ductus. Definitive closure can be accomplished by surgical division or ligation of the ductus or by transcatheter techniques in which an occluding device is placed.

Congenital Aortic Stenosis

Congenital aortic stenosis (AS) is most often caused by abnormal structural development of the valve leaflets. It occurs in 5 of 10,000 live births and is four times as common in males as in females. Twenty percent of patients have an additional abnormality, most commonly coarctation of the aorta (discussed later). The aortic valve in congenital AS usually has a **bicuspid** leaflet structure instead of the normal three-leaflet configuration, causing an eccentric stenotic opening through which blood is ejected. Most bicuspid aortic valves are actually nonobstructive at birth and therefore only rarely result in congenital AS. More often, bicuspid valves become progressively stenotic over a great many years, as the leaflets progressively fibrose and calcify, and represent a common cause of AS in adults (see Chapter 8).

Pathophysiology

Because the valvular orif ce is signif cantly narrowed, left ventricular systolic pressure must increase to pump blood across the valve into the aorta. In response to this increased pressure load, the LV hypertrophies (Fig. 16-14). The high-velocity jet of blood that passes through the stenotic valve may impact the proximal aortic wall and contribute to dilatation of that vessel.

Symptoms

The clinical picture of AS depends on the severity of the lesion. Fewer than 10% of infants experience symptoms of heart failure before age 1, but if they do, they manifest tachycardia, tachypnea, failure to thrive, and poor feeding. Most older children with congenital AS are asymptomatic and develop normally. When symptoms do occur, they are similar to those of adult AS and include fatigue, exertional dyspnea, angina pectoris, and syncope (see Chapter 8).

Physical Examination

Auscultation reveals a harsh crescendo–decrescendo systolic murmur, loudest at the base of the heart with radiation toward the neck. It is often preceded by a systolic ejection click (see Chapter 2), especially when a bicuspid valve is present. Unlike the murmurs of ASD, VSD, or PDA, the murmur of congenital AS is characteristically present from birth because it does not depend on the postnatal decline in pulmonary vascular resistance. With advanced disease, the ejection time becomes longer, causing the peak of the murmur to occur later in systole. In severe disease, the signif cantly prolonged ejection time causes a delay in closure of the aortic valve such that A_2 occurs after P_2—a phenomenon known as reversed splitting (also termed "paradoxical splitting") of S_2 (see Chapter 2).

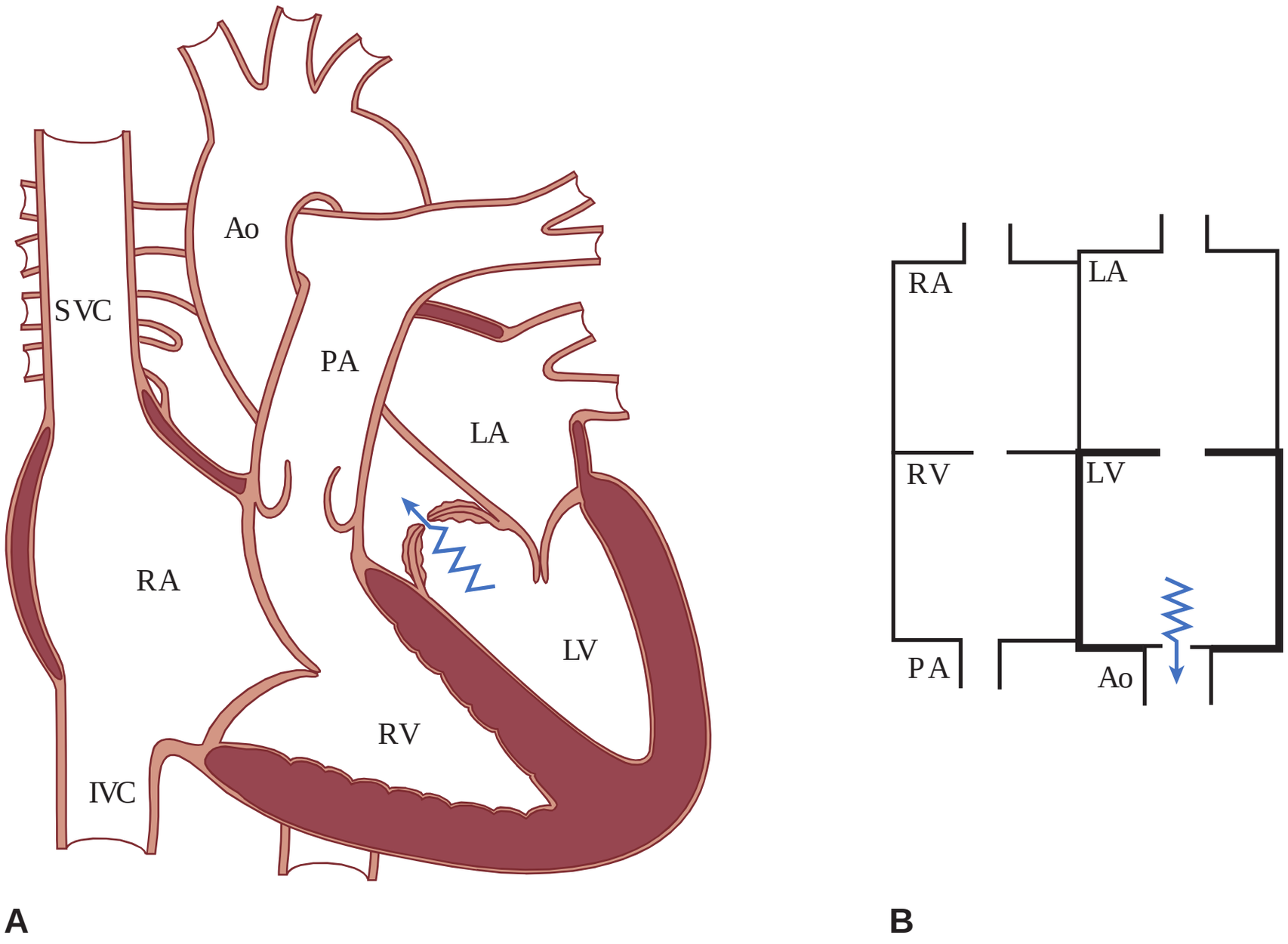

FIGURE 16-14. Congenital aortic valve stenosis. A. The jagged arrow traverses the narrowed aortic valve. **B.** Schematic representation of obstructed f ow through the narrowed aortic valve (jagged arrow). Left ventricular (LV) hypertrophy results from the chronically increased pressure load. Poststenotic dilatation of the aorta (Ao) is common. IVC, inferior vena cava; LA, left atrium; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Diagnostic Studies

The chest radiograph of an infant with AS may show an enlarged LV and a dilated ascending aorta. The ECG often shows left ventricular hypertrophy. Echocardiography identifies the abnormal structure of the aortic valve and the degree of left ventricular hypertrophy. Doppler assessment can accurately measure the pressure gradient across the stenotic valve and allow calculation of the valve area. Cardiac catheterization confirms the pressure gradient across the valve.

Treatment

In its milder forms, congenital AS does not need to be corrected but should be followed closely as the degree of stenosis may worsen over time. Severe obstruction of the aortic valve during infancy may mandate immediate repair. Transcatheter balloon valvuloplasty is the first line of intervention, but surgical repair may be necessary if valvuloplasty fails to relieve the obstruction or if significant aortic regurgitation results from balloon dilation. Often, valvuloplasty in infancy is only palliative, and repeat catheter balloon dilation or surgical revision is needed later.

Pulmonic Stenosis

Obstruction to right ventricular outflow may occur at the level of the pulmonic valve (e.g., from congenitally fused valve commissures), within the body of the RV (i.e., in the RV outflow tract), or in the pulmonary artery. Valvular pulmonic stenosis is the most frequent form (Fig. 16-15).

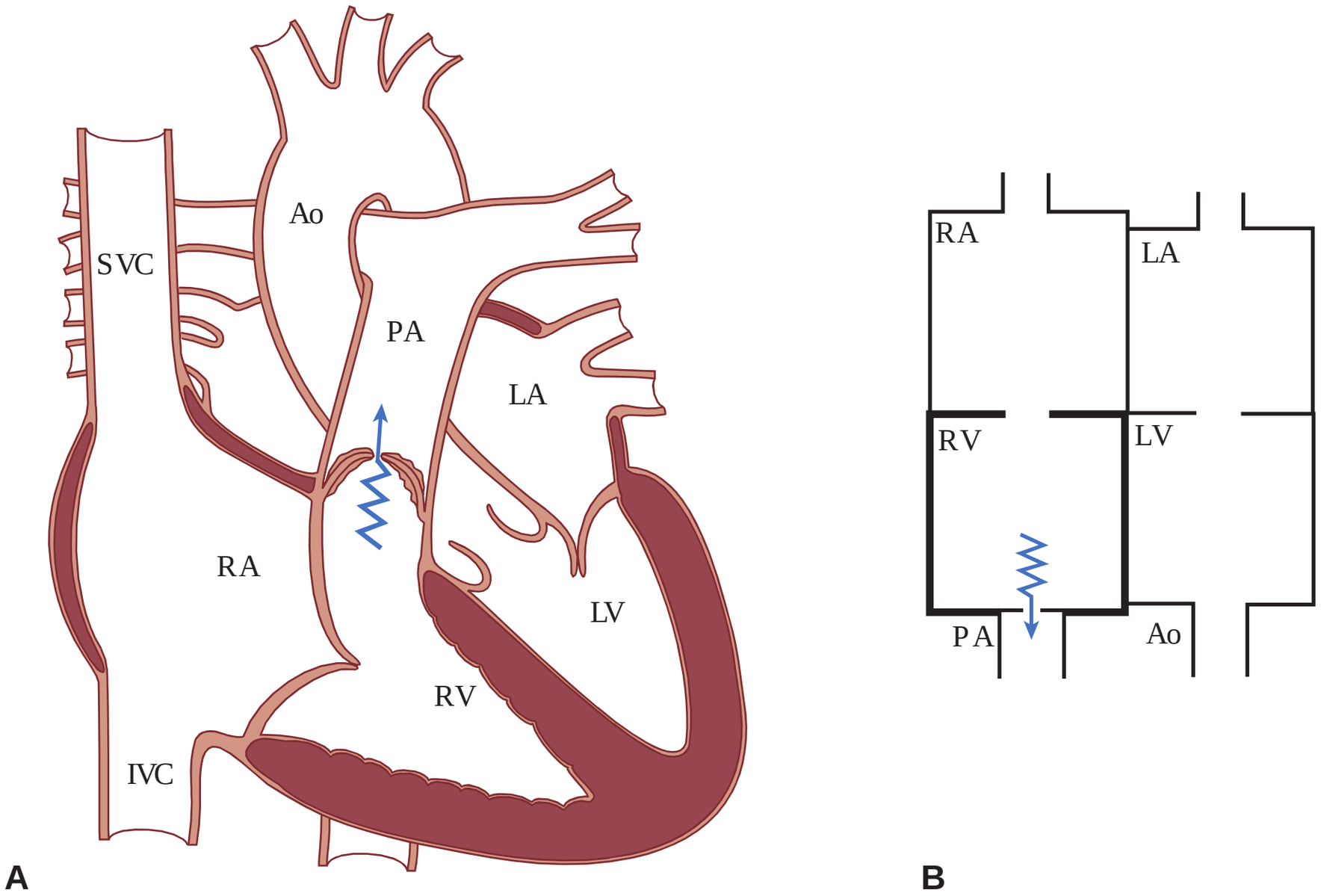

FIGURE 16-15. Congenital pulmonary valve stenosis. A. The jagged arrow traverses the narrowed pulmonary valve. **B.** Schematic representation of obstructed flow through the narrowed pulmonary valve (jagged arrow). Right ventricular hypertrophy results from the chronically increased pressure load. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

Pathophysiology

The consequence of pulmonic stenosis is impairment of right ventricular outflow, which leads to increased RV pressures and chamber hypertrophy. The clinical course is determined by the severity of the obstruction. Although mild pulmonic stenosis rarely progresses and is unlikely to affect RV function, untreated severe pulmonic stenosis typically results in right-sided heart failure.

Symptoms

Children with mild or moderate pulmonary stenosis are asymptomatic. The diagnosis is often first made on discovery of a murmur during a routine physical examination. Severe stenosis may cause manifestations such as dyspnea with exertion, exercise intolerance, and with decompensation, symptoms of right-sided heart failure such as abdominal fullness and pedal edema.

Physical Examination

The physical findings in pulmonic stenosis depend on the severity of the obstruction. If the stenosis is severe with accompanying right ventricular hypertrophy, a prominent jugular venous a wave can be observed (see Chapter 2) and an RV heave is palpated over the sternum. A loud, late-peaking, crescendo–decrescendo systolic ejection murmur is heard at the upper left sternal border, often associated with a palpable thrill. Widened splitting of the S_2 with a soft P_2 component is caused by the delayed closure of the stenotic pulmonary valve.

In more moderate stenosis, a pulmonic ejection sound (a high-pitched "click") follows S_1 and precedes the systolic murmur. It occurs during the early phase of right ventricular contraction as the stenotic valve leaflets suddenly reach their maximum level of ascent into the pulmonary artery, just before blood ejection. Unlike other sounds and murmurs produced by the right side of the heart, the pulmonic ejection sound diminishes in intensity during inspiration. This occurs because with inspiration, the augmented right-sided filling elevates the leaflets into the pulmonary artery prior to RV contraction, preempting the rapid tensing in early systole that is thought to produce the sound.

Diagnostic Studies

The chest radiograph may demonstrate an enlarged right atrium and ventricle with poststenotic pulmonary artery dilation (thought to be caused by the impact of the high-velocity jet of blood against the wall of the pulmonary artery). The ECG shows right ventricular hypertrophy with right axis deviation. Echocardiography with Doppler imaging assesses the pulmonary valve morphology, determines the presence of right ventricular hypertrophy, and accurately measures the pressure gradient across the obstruction.

Treatment

Mild pulmonic stenosis usually does not progress or require treatment. Moderate or severe valvular obstruction at the valvular level can be relieved by dilating the stenotic valve by means of transcatheter balloon valvuloplasty. Long-term results of this procedure have been uniformly excellent, and right ventricular hypertrophy usually regresses subsequently.

Coarctation of the Aorta

Coarctation of the aorta typically consists of a discrete narrowing of the aortic lumen (Fig. 16-16). This anomaly has an incidence of 1 in 6,000 live births, and the most common associated cardiac abnormality is a bicuspid aortic valve. Aortic coarctation often occurs in patients with Turner syndrome (45, XO).

In the past, coarctations were described as either "preductal" (infantile) or "postductal" (adult-type) based on the location of the aortic narrowing in relation to the ductus arteriosus. These terms have been largely abandoned because the vast majority of coarctations are actually juxtaductal (i.e., "next to" the ductus) and etiologic differences between the preductal and postductal categories have not been substantiated.

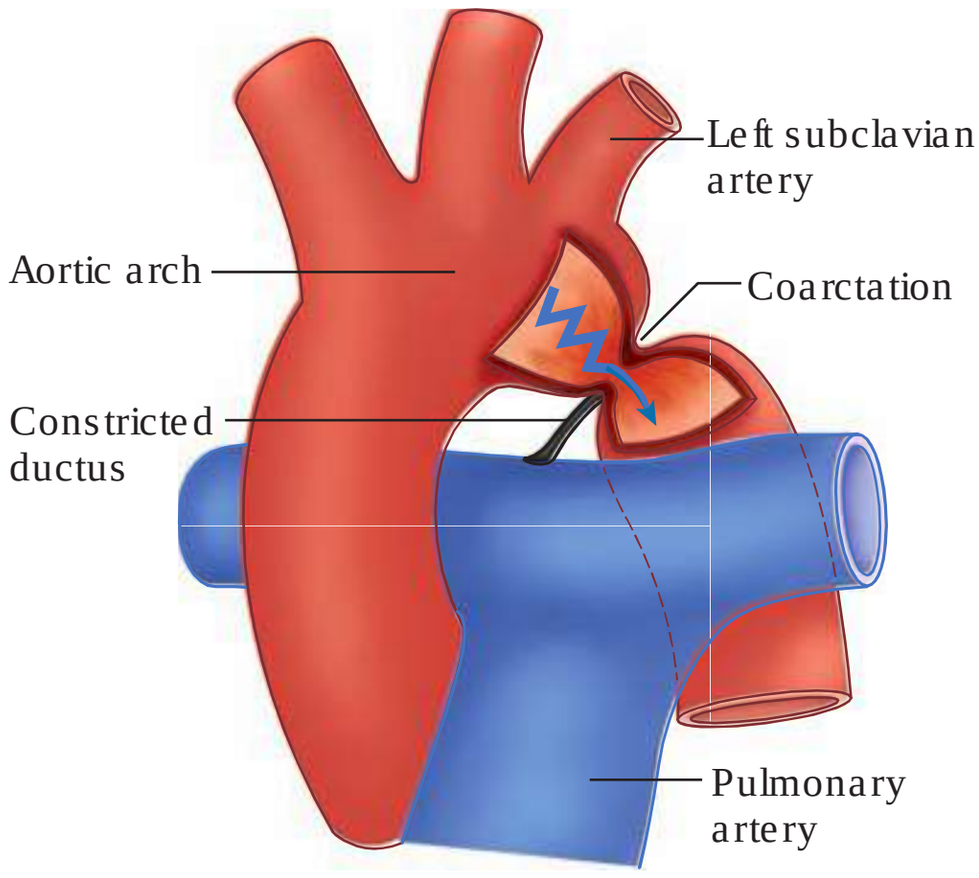

FIGURE 16-16. Coarctation of the aorta. A pressure gradient is present across the narrowed lumen of the aorta.

While the actual pathogenesis of aortic coarctation has not been defined, one theory contends that reduced antegrade blood flow through the left side of the heart and ascending aorta during fetal life leads to hypoplastic development of the aorta ("no flow, no grow"). Another theory is that ectopic muscular ductus arteriosus tissue extends into the aorta during fetal life and constricts following birth at the same time the ductus is caused to close. More recent evidence suggests that aortic coarctation may be just one manifestation of a more diffuse aortic disease.

Pathophysiology

Because of the impedance of aortic narrowing in coarctation, the LV faces an increased afterload. Blood flow to the head and upper extremities is preserved because the vessels supplying these areas usually branch off the aorta proximal to the obstruction, but flow to the descending aorta and lower extremities may be diminished. If coarctation is not corrected, compensatory alterations include (1) development of left ventricular hypertrophy and (2) dilatation of collateral blood vessels from the intercostal arteries that bypass the coarctation and provide blood to the more distal descending aorta. Eventually, these collateral vessels enlarge and can erode the undersurface of the ribs.

Symptoms

Patients with severe coarctation usually present very shortly after birth with symptoms of heart failure. Infants may also exhibit differential cyanosis if the ductus arteriosus fails to constrict and remains patent. The upper half of the body, supplied by the LV and the ascending aorta, is perfused with well-oxygenated blood; however, the lower half appears cyanotic because it is largely supplied by right-to-left flow of poorly oxygenated blood from the pulmonary artery, across the PDA, and into the descending aorta, beyond the coarctation.

When the coarctation is less severe, a patient may be asymptomatic or experience only mild weakness or pain in the lower extremities following exercise (i.e., claudication). In asymptomatic cases, coarctation may be suspected by the finding of upper extremity hypertension later in life (see Chapter 13).

Physical Examination

On examination, the femoral pulses are weak and delayed. An elevated blood pressure in the upper body is the most common finding. If the coarctation occurs distal to the takeoff of the left

subclavian artery, the systolic pressure in the arms is greater than that in the legs. If the coarctation occurs proximal to the takeoff of the left subclavian artery, the systolic pressure in the right arm may exceed that in the left arm. A systolic pressure in the right arm that is 15 to 20 mm Hg greater than that in a leg is sufficient to suspect coarctation, because normally the systolic pressure in the legs is higher than that in the arms. A midsystolic ejection murmur (caused by turbulent flow through the coarctation) may be audible over the chest and/or back. A prominent tortuous collateral arterial circulation may create continuous murmurs over the chest in adults.

Diagnostic Studies

In adults with uncorrected coarctation of the aorta, chest radiography generally reveals notching of the inferior surface of the posterior ribs owing to enlarged intercostal vessels supplying collateral circulation to the descending aorta. An indented aorta at the site of coarctation may also be visualized. The ECG shows left ventricular hypertrophy resulting from the pressure load placed on that chamber. Doppler echocardiography confirms the diagnosis of coarctation and assesses the pressure gradient across the lesion. Magnetic resonance (or CT) imaging demonstrates in detail the length and severity of coarctation (see Fig. 16-17). Diagnostic catheterization and angiography are rarely necessary.

Treatment

In neonates with severe obstruction, prostaglandin infusion is administered to keep the ductus arteriosus patent, thus maintaining blood flow to the descending aorta before surgery is undertaken. In children, elective repair is usually performed to prevent systemic hypertension. Several effective surgical procedures are available, including excision of the narrowed aortic segment with end-to-end reanastomosis and direct repair of the coarctation, sometimes using synthetic patch material. For older children, adults, and patients with recurrent coarctation after previous repair, transcatheter interventions (balloon dilatation with or without stent placement) are usually successful.

Cyanotic Lesions

Tetralogy of Fallot

Tetralogy of Fallot results from a single developmental defect: an abnormal anterior and cephalad displacement of the infundibular (outflow tract) portion of the interventricular septum. As a consequence, four anomalies arise that characterize this condition, as shown in Figure 16-18: (1) a VSD caused by anterior malalignment of the interventricular septum, (2) subvalvular pulmonic stenosis because of obstruction from the displaced infundibular septum (often with valvular pulmonic stenosis), (3) an overriding aorta that receives blood from both ventricles, and (4) right ventricular hypertrophy owing to the high-pressure load placed on the RV by the pulmonic stenosis. Tetralogy of Fallot is the most common form of cyanotic congenital heart disease after

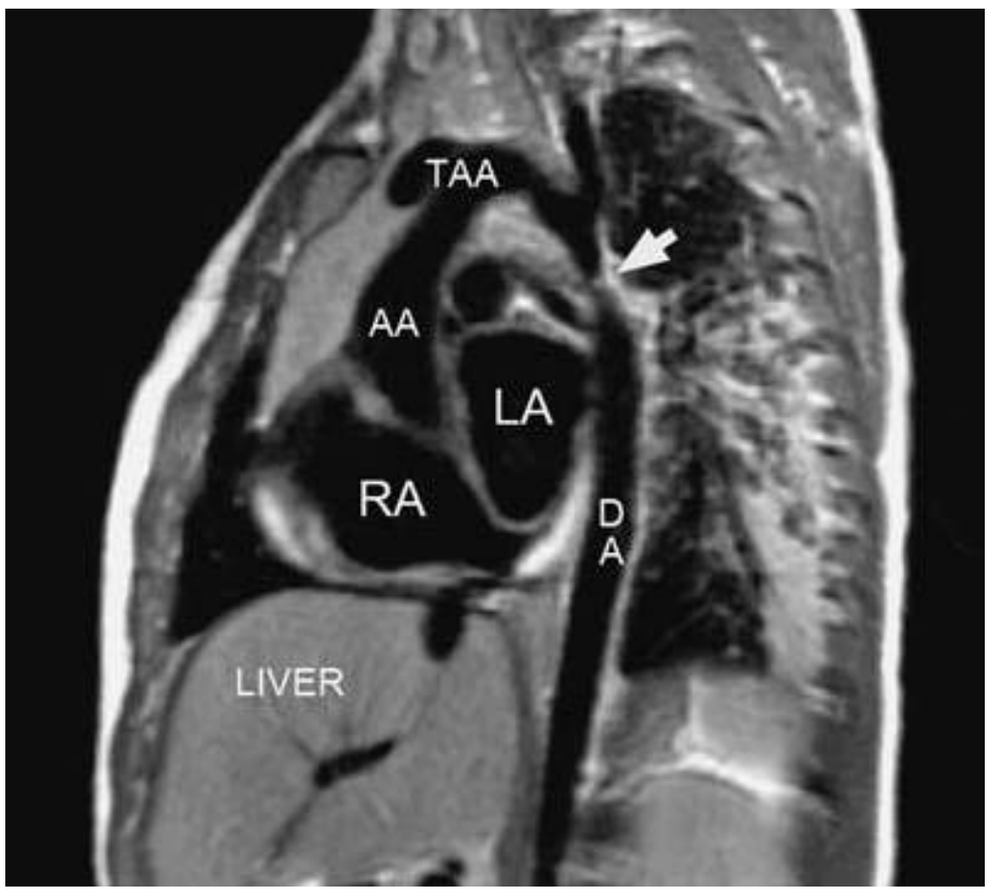

FIGURE 16-17. Magnetic resonance imaging of coarctation of the aorta. This lateral view demonstrates coarctation, manifest as a focal aortic narrowing (white arrow). AA, ascending aorta; DA, descending aorta; LA, left atrium; RA, right atrium; TAA, transverse aortic arch.

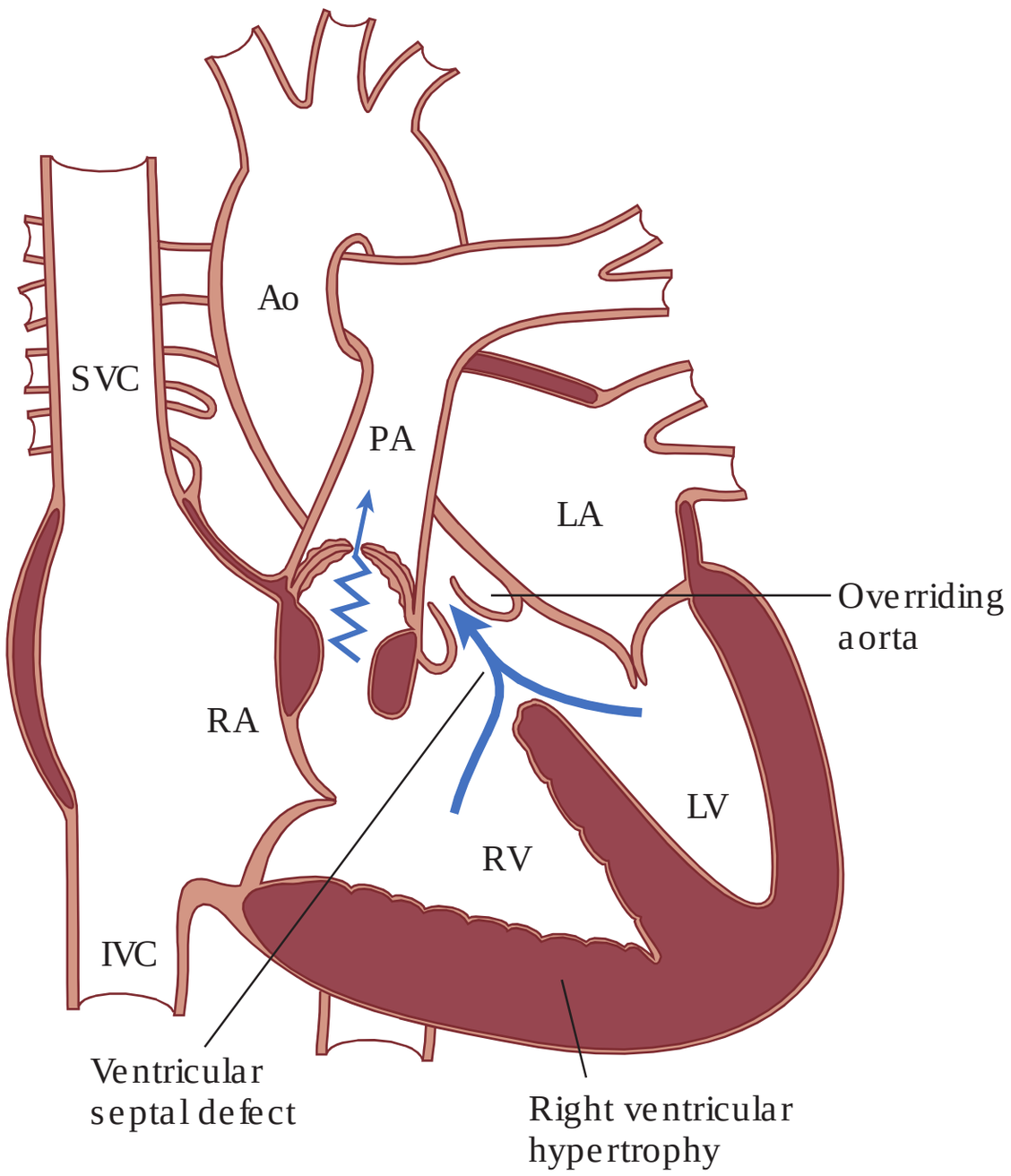

FIGURE 16-18. Tetralogy of Fallot is characterized by four associated anomalies. (1) A ventricular septal defect, (2) obstruction to right ventricular outflow (jagged arrow), (3) an overriding aorta that receives blood from both ventricles, and (4) right ventricular hypertrophy. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

infancy, occurring in 5 of 10,000 live births and is often associated with other cardiac defects, including a right-sided aortic arch (25% of patients), ASD (10% of patients), and less often, an anomalous origin of the left coronary artery. A microdeletion in chromosome 22 (22q11) has been identified in patients with a syndrome that includes tetralogy of Fallot as one of the cardiovascular manifestations (see Box 16-1).

BOX 16-1 Genetic Abnormalities in Congenital Heart Disease

Progress in understanding of genetic influences on cardiac development and congenital heart disease is proceeding at a brisk pace. Although nearly all cardiac congenital anomalies can occur as isolated findings, the clustering of certain forms with heritable syndromes and known genetic abnormalities provides clues to the underlying basis of certain defects.

Among infants with **Down syndrome** (trisomy 21), the incidence of congenital heart defects is nearly 40%. Many of these are common abnormalities such as ASDs, VSDs, and PDAs. There is also a high incidence of a rarer condition known as common AV canal, which consists of a large primum ASD and VSD and a common (undivided) AV valve. These central heart structures are usually formed by the endocardial cushions and cells of neural crest origin, which are known to have abnormal migration patterns in patients with trisomy 21.

Turner syndrome (45, XO) is another heritable condition associated with congenital heart disease. Left-sided obstructive congenital heart lesions are common in patients with this syndrome, including bicuspid aortic valve, coarctation of the aorta, and occasionally hypoplastic left heart syndrome (underdevelopment of the LV and aorta). The specific genes responsible for these abnormalities have not yet been elucidated.

In contrast, discrete gene abnormalities have been identified in other syndrome-associated forms of congenital heart disease. Many patients with **Williams syndrome** (characterized by mental retardation, hypercalcemia, renovascular hypertension, facial abnormalities, and short stature) have supravalvular AS, and some have a more diffuse arteriopathy of the aorta as well as pulmonary artery obstruction. The genetic abnormality in Williams syndrome is a deletion on chromosome 7

BOX 16-1 Genetic Abnormalities in Congenital Heart Disease (continued)

(7q11.23), a region that includes the elastin gene. Abnormalities in the production of elastin, a critical component of the arterial wall, may be responsible for the observed arteriopathy.

DiGeorge syndrome (characterized by pharyngeal defects, hypocalcemia due to absent parathyroid glands, and T-cell dysfunction secondary to hypoplasia of the thymus) is associated with congenital abnormalities of the cardiac outflow tracts, including tetralogy of Fallot, truncus arteriosus (a large VSD over which a single large outflow vessel arises), and interrupted aortic arch. Most patients with DiGeorge syndrome have a microdeletion within chromosome 22 (22q11), a region that contains the TBX1 gene. This gene encodes a transcription factor that appears to play a critical role in developmental patterning of the cardiac outflow tracts.

CHARGE syndrome (the acronym for **c**oloboma [congenital absence of portions of eye structures], **h**eart defects, choanal **a**tresia [nasal passage obstruction], **r**etardation of growth and development, **g**enitourinary malformation, **e**ar abnormalities) is an autosomal dominant disorder that includes some or all of the listed components. Associated cardiac abnormalities include interrupted aortic arch, tetralogy of Fallot, double outlet right ventricle, and AV septal defects. The incidence of the syndrome is approximately 1:10,000 children, and most are found to have a mutation or microdeletion in the CHD7 gene, the protein product of which is a transcription regulator associated with several tissue-specific target genes.

Several other transcription factors involved in heart development likely contribute to congenital heart disease. Some families with heritable forms of ASDs have mutations in the transcription factor gene Nkx2.5. An associated transcription factor gene GATA4 appears to collaborate with Nkx2.5 and has also been implicated in familial septal defect syndromes. Mutations in TBX5, yet another transcription factor gene, are responsible for **Holt–Oram syndrome** (also known as the heart–hand syndrome), an autosomal dominant disorder whose characteristic cardiac defects include secundum ASDs and VSDs.

Further deciphering of the genome will undoubtedly improve understanding of cardiac development and the molecular defects that lead to congenital heart abnormalities.

Pathophysiology

Increased resistance by the subvalvular pulmonic stenosis causes deoxygenated blood returning from the systemic veins to be diverted from the RV, through the VSD to the LV, and into the systemic circulation, resulting in systemic hypoxemia and cyanosis. The magnitude of shunt flow across the VSD is primarily a function of the severity of the pulmonary stenosis, but acute changes in systemic and pulmonary vascular resistances can affect it as well.

Symptoms

Children with tetralogy of Fallot often experience dyspnea on exertion. "Spells" may occur following exertion, feeding, or crying when systemic vasodilatation results in an increased right-to-left shunt. Manifestations of such spells include irritability, cyanosis, hyperventilation, and occasionally syncope or convulsions. Children learn to alleviate their symptoms by squatting down, which is thought to increase systemic vascular resistance by "kinking" the femoral arteries, thereby decreasing the right-to-left shunt and directing more blood from the RV to the lungs.

Physical Examination

Children with tetralogy of Fallot and moderate pulmonary stenosis often have mild cyanosis, most notably of the lips, mucous membranes, and digits. Infants with severe pulmonary stenosis may present with profound cyanosis in the first few days of life. Chronic hypoxemia

caused by the right-to-left shunt commonly results in clubbing of the fingers and toes. Right ventricular hypertrophy may be appreciated on physical examination as a palpable heave along the left sternal border. The S_2 is single, composed of a normal aortic component; the pulmonary component is soft and usually inaudible. A systolic ejection murmur heard best at the upper left sternal border is created by turbulent blood flow through the stenotic right ventricular outflow tract. There is usually no distinct murmur related to the VSD, because it is typically large and thus generates little turbulence.

Diagnostic Studies

Chest radiography demonstrates prominence of the RV and decreased size of the main pulmonary artery segment, giving the appearance of a "boot-shaped" heart. Pulmonary vascular markings are typically diminished because of decreased flow through the pulmonary circulation. The ECG shows right ventricular hypertrophy with right axis deviation. Echocardiography details the right ventricular outflow tract anatomy, the malaligned VSD, right ventricular hypertrophy, and other associated defects, as does cardiac catheterization.

Treatment

Before definitive surgical correction of tetralogy of Fallot was developed, several forms of palliative therapy were undertaken. These involved creating anatomic communications between the aorta (or one of its major branches) to the pulmonary artery, establishing a left-to-right shunt to increase pulmonary blood flow. Such procedures are occasionally used today in infants for whom definitive repair is planned at an older age. Complete surgical correction of tetralogy of Fallot involves closure of the VSD and enlargement of the subpulmonary infundibulum with the use of a pericardial patch. Elective repair is usually recommended at 6 to 12 months of age to decrease the likelihood of future complications. Most patients who have undergone successful repair grow to become asymptomatic adults. However, antibiotic prophylaxis to prevent endocarditis is required in some patients (see Chapter 8).

Transposition of the Great Arteries

In transposition of the great arteries (TGAs), each great vessel inappropriately arises from the opposite ventricle; that is, the aorta originates from the RV and the pulmonary artery originates from the LV (Fig. 16-19). This anomaly accounts for approximately 7% of congenital heart defects, affecting 40 of 100,000 live births. Whereas tetralogy of Fallot is the most common etiology of cyanosis after infancy, TGA is the most common cause of cyanosis in the neonatal period.

The precise cause of transposition remains unknown. One theory contends that failure of the aorticopulmonary septum to spiral in a normal fashion during fetal development is the underlying problem. It

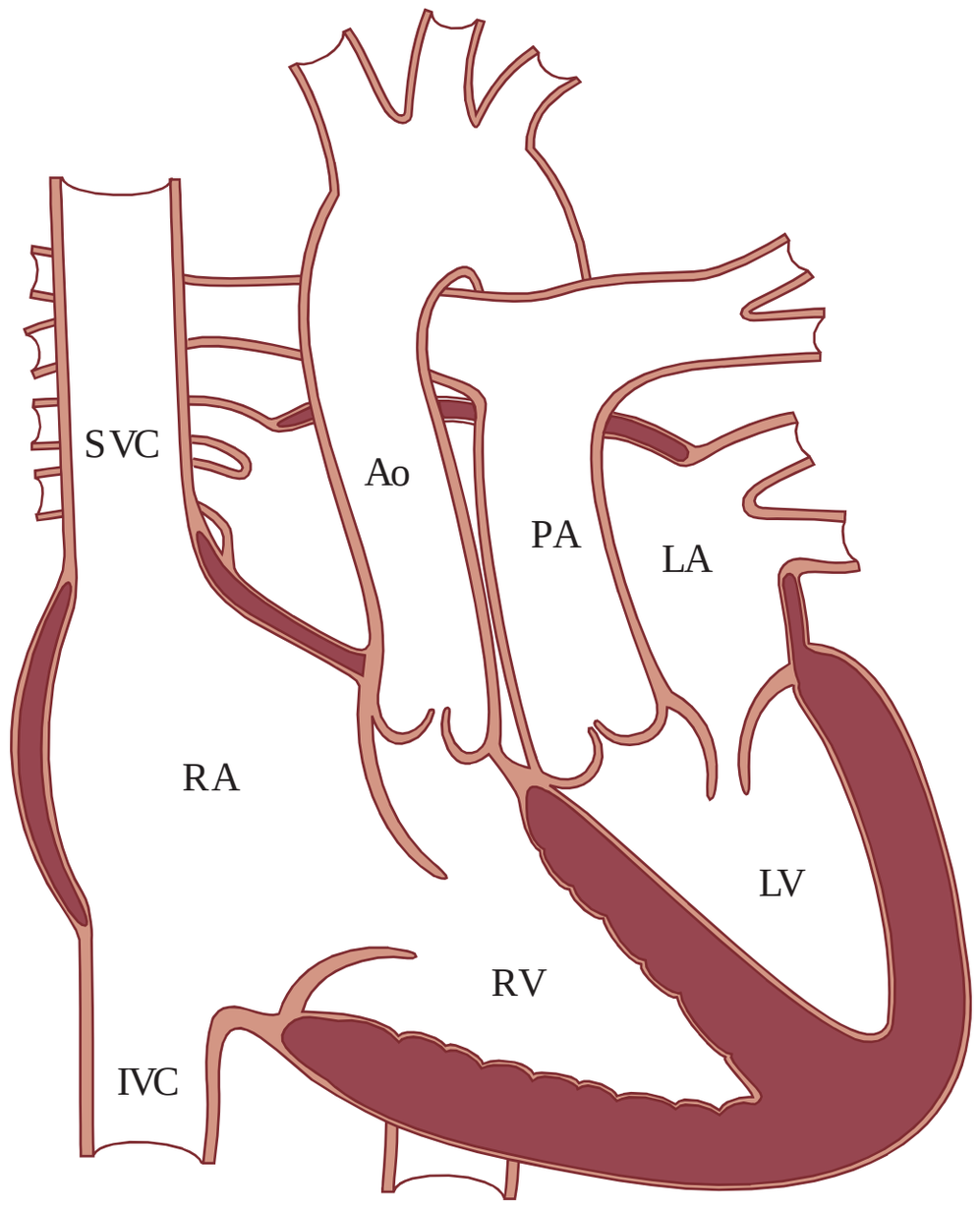

FIGURE 16-19. Transposition of the great arteries. The aorta (Ao) and pulmonary artery (PA) arise abnormally from the right ventricle (RV) and left ventricle (LV), respectively. IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava.

has also been suggested that the defect may be the result of abnormal growth and absorption of the subpulmonary and subaortic infundibuli during the division of the truncus arteriosus. Normally, reabsorption of the subaortic infundibulum places the forming aortic valve posterior and inferior to the pulmonary valve and in continuity with the LV. In TGA, the process of infundibular reabsorption may be reversed, placing the pulmonary valve over the LV instead.

Pathophysiology

TGA separates the pulmonary and systemic circulations by placing the two circuits in parallel rather than in series. This arrangement forces desaturated blood from the systemic venous system to pass through the RV and then return to the systemic circulation through the aorta without undergoing normal oxygenation in the lungs. Similarly, oxygenated pulmonary venous return passes through the LV and then back through the pulmonary artery to the lungs without imparting oxygen to the systemic circulation. The result is an extremely hypoxic, cyanotic neonate. Without intervention to create mixing between the two circulations, TGA is a lethal condition.

TGA is compatible with life in utero because flow through the ductus arteriosus and foramen ovale allows communication between the two circulations. Oxygenated fetal blood flows from the placenta through the umbilical vein to the right atrium, and then most of it travels into the left atrium through the foramen ovale. The oxygenated blood in the left atrium passes into the LV and is pumped out the pulmonary artery. Most of the pulmonary artery flow travels through the ductus arteriosus into the aorta, instead of the high-resistance pulmonary vessels, such that oxygen is provided to the developing tissues.

After birth, normal physiologic closure of the ductus and the foramen ovale eliminates the shunt between the parallel circulations and, without intervention, would result in death because oxygenated blood does not reach the systemic tissues. However, if the ductus arteriosus and foramen ovale remain patent (either naturally or with exogenous prostaglandins or surgical intervention), communication between the parallel circuits is maintained, and sufficiently oxygenated blood may be provided to the brain and other vital organs.

Symptoms and Physical Examination

Infants with transposition appear blue, with the intensity of the cyanosis dependent on the degree of intermixing between the parallel circuits. In most cases, generalized cyanosis is apparent on the first day of life and progresses rapidly as the ductus arteriosus closes. Palpation of the chest reveals a right ventricular impulse at the lower sternal border as the RV faces systemic pressures. Auscultation may reveal an accentuated S_2, which reflects closure of the anteriorly placed aortic valve just under the chest wall. Prominent murmurs are uncommon and may signal an additional defect.

Diagnostic Studies

Chest radiography is usually normal, although the base of the heart may be narrow owing to the more anterior–posterior orientation of the aorta and pulmonary artery. The ECG demonstrates right ventricular hypertrophy, reflecting the fact that the RV is the systemic "high-pressure" pumping chamber. The definitive diagnosis of transposition can be made by echocardiography, which demonstrates the abnormal orientation of the great vessels.

Treatment

TGA is a medical emergency. Initial treatment includes maintenance of the ductus arteriosus by prostaglandin infusion and creation of an interatrial communication using a balloon catheter (termed the Rashkind procedure). Such intervention allows adequate mixing of the two

circulations until definitive corrective surgery can be performed. The current corrective procedure of choice is the "arterial switch" operation (Jatene procedure), which involves transection of the great vessels above the semilunar valves and origin of the coronary arteries. The great vessels are then reversed to the natural configuration, so the aorta arises from the LV and the pulmonary artery arises from the RV. The coronary arteries are then relocated to the new aorta.

EISENMENGER SYNDROME

Eisenmenger syndrome is the condition of severe pulmonary vascular obstruction that results from chronic left-to-right shunting through a congenital cardiac defect. The elevated pulmonary vascular resistance causes reversal of the original shunt (to the right-to-left direction) and systemic cyanosis.

The mechanism by which increased pulmonary f ow causes this condition is unknown. Histologically, the pulmonary arteriolar media hypertrophies and the intima proliferates, reducing the cross-sectional area of the pulmonary vascular bed. Over time, the vessels become thrombosed, and the resistance of the pulmonary vasculature rises, causing the original left-to-right shunt to decrease. Eventually, if the resistance of the pulmonary circulation exceeds that of the systemic vasculature, the direction of shunt f ow reverses.

With reversal of the shunt to the right-to-left direction, symptoms arise from hypoxemia, including exertional dyspnea and fatigue. Reduced hemoglobin saturation stimulates the bone marrow to produce more red blood cells (erythrocytosis), which can lead to hyperviscosity, symptoms of which include fatigue, headaches, and stroke (caused by cerebrovascular occlusion). Infarction or rupture of the pulmonary vessels can result in hemoptysis.

On examination, a patient with Eisenmenger syndrome appears cyanotic with digital clubbing. A prominent a wave in the jugular venous pulsation ref ects elevated right-sided pressure during atrial contraction. A loud P_2 is common. The murmur of the inciting left-to-right shunt is usually absent, because the original pressure gradient across the lesion is negated by the elevated right-heart pressures.

Chest radiography in Eisenmenger syndrome is notable for proximal pulmonary artery dilatation with peripheral tapering. Calcification of the pulmonary vasculature may be seen. The ECG demonstrates right ventricular hypertrophy and right atrial enlargement. Echocardiography with Doppler studies can usually identify the underlying cardiac defect and quantitate the pulmonary artery systolic pressure.

Treatment includes the avoidance of activities that can exacerbate the right-to-left shunt. These include strenuous physical activity, high altitude, and the use of peripheral vasodilator drugs. Pregnancy is especially dangerous; the rate of spontaneous abortion is 20% to 40%, and the incidence of maternal mortality is approximately 45%. Supportive measures for Eisenmenger syndrome include prompt treatment of infections, management of rhythm disturbances, and phlebotomy for patients with symptomatic erythrocytosis.

Although there are no remedies that reverse the disease process in Eisenmenger syndrome, pulmonary vasodilator therapy can provide symptomatic relief and improve the patient's quality of life. Effective agents include endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase inhibitors (see Chapter 17). The only effective long-term strategy for severely affected patients is lung or heart–lung transplantation. Fortunately, with the dramatic advances that have been made in the detection and early correction of severe congenital heart defects, Eisenmenger syndrome has become less common.

SUMMARY

- Formation of the cardiovascular system begins during the 3rd week of embryonic development; soon after, a unique circulation develops that allows the fetus to mature in the uterus, using the placenta as the primary organ of gas, nutrient, and waste exchange.

- At birth, the fetal lungs inf ate and become functional, making the placenta unnecessary and altering circulation patterns to allow the neonate to adjust to life outside the womb.
- Cardiac malformations occur in 0.8% of live births, representing the most common form of birth defects and the leading cause of death from birth abnormalities in the first year of life.
- Congenital heart lesions can be grouped into cyanotic or acyanotic defects, depending on whether the abnormality results in right-to-left shunting of blood.
- Acyanotic defects often result in either volume overload (ASD, VSD, PDA) or pressure overload (AS, pulmonic stenosis, coarctation of the aorta).
- Chronic volume overload resulting from a large left-to-right shunt can ultimately result in increased pulmonary vascular resistance, reversal of the direction of shunt f ow, and subsequent cyanosis (Eisenmenger syndrome).
- Among the most common cyanotic defects are tetralogy of Fallot and transposition of the great arteries.

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