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امنیـت اطلاعـات

یکبـار پـرداخت

The Cardiovascular System

PART XVIII

Section 1

Developmental Biology of the Cardiovascular System

Chapter 469

Cardiac Development

Daniel Bernstein and William R. Goodyer

INTRODUCTION

Cardiac defects have traditionally been grouped by common morphologic patterns: for example, **abnormalities of the outflow tracts** (conotruncal lesions such as tetralogy of Fallot and truncus arteriosus) and **abnormalities of atrioventricular septation** (primum atrial septal defect, atrioventricular septal defect). These morphologic categories may be revised or eventually supplanted by new categories as our understanding of the genetic and molecular basis of congenital heart disease progresses.

469.1 Early Cardiac Morphogenesis

Daniel Bernstein and William R. Goodyer

In the early presomite embryo, the first identifiable cardiac progenitor cell clusters migrate from the primitive streak and are arranged in the anterior lateral plate mesoderm on both sides of the embryo's central axis in a horseshoe pattern, also known as the *cardiac crescent*. These cell clusters are marked by their expression of the basic helix-loop-helix (bHLH) transcription factor mesoderm posterior 1 (MESP1) and subsequently form paired cardiac tubes by 18 days of gestation. This *cardiac progenitor zone* is shaped by a balanced gradient of positive and negative signals arising from the tissues surrounding the cardiac mesodermal cells, with signals from the surrounding ventral/lateral tissues promoting cardiogenesis through signaling molecules such as bone morphogenetic protein (BMP), sonic hedgehog (SHH), and fibroblast growth factor 8 (FGF8) and signals from dorsal/medial structures such as members of the canonical Wnt/β-catenin pathway inhibiting cardiogenesis. Cardiogenic signals activate the genetic expression of cardiac-specific transcription factors (e.g., *TBX, GATA, NKX2.5*) to activate developmental cardiac gene expression The paired tubes fuse in the midline on the ventral surface of the embryo to form the primitive *heart tube* by 22 days. This straight heart tube is composed of an outer myocardial layer, an inner endocardium, and a middle layer of extracellular matrix (ECM) known as the *cardiac jelly*. There are two distinct cell lineages: the **first heart field** (regulated mainly by *NKX2.5*) provides precursor cells for the left ventricle and parts of the atria; the **second heart field** (regulated mainly by *ISL1*) provides precursors for the right ventricle, outflow tracts, and caudal aspects of the atria. Premyocardial cells, including epicardial cells and cells derived from the neural crest, continue their migration into the region of the heart tube. Regulation of this early phase of cardiac morphogenesis is controlled in part by the interaction of specific signaling molecules or ligands, usually expressed by one cell type, with specific receptors, usually expressed by another cell type. Positional information is conveyed to the developing cardiac mesoderm by factors such as *retinoids* (isoforms of vitamin A), which bind to specific nuclear receptors and regulate gene transcription. Migration of epithelial cells into the developing heart tube is directed by ECM proteins (e.g., fibronectin) that interact with cell surface receptors (the *integrins*). The clinical importance of these signaling pathways is revealed by the spectrum of **cardiac teratogenic effects** caused by the retinoid-like drug isotretinoin.

As early as 20-22 days, before cardiac looping, the embryonic heart begins to contract and exhibit phases of the cardiac cycle that are surprisingly similar to those in the mature heart. Morphologists initially identified segments of the heart tube that were believed to correspond to structures in the mature heart (Fig. 469.1). The *sinus venosus* (systemic venous system and part of right atrium), *primitive atrium* (right and left atria), *primitive ventricle* (left ventricle), and *bulbus cordis* that can be broken down into three sections (the proximal one third, right ventricle; mid-third, conus cordis to outflow tracts; and distal third, truncus arteriosus to aorta and pulmonary artery). However, this model is oversimplified. Only the **trabecular** (most heavily muscularized) portions of the left ventricular myocardium are present in the early cardiac tube; the cells that will become the inlet portion of the left ventricle migrate into the cardiac tube at a later stage (after looping is initiated). Even later to appear are the primordial cells that give rise to the great arteries (truncus arteriosus), including cells derived from the neural crest, which are not present until after cardiac looping is complete. Chamber-specific transcription factors participate in the differentiation of atria from ventricles and in the right and left ventricles. The bHLH transcription factor gene *(HAND2)* is expressed in the developing right ventricle. Disruption of this gene or of other transcriptional factors such as *MEF2c* in mice leads to hypoplasia of the right ventricle. Other genetic markers of the second heart field (early right ventricle) cells include *IRX4, TBX20, ISL1, TNNT2, MLC2v,* and *TBX1*. The transcription factor *HAND1* is expressed in the developing left ventricle and conotruncus and is also critical to their development. Other genetic markers of the first heart field (early left ventricle) cells include *TBX5, NKX2.5, TNNT2, MLC2v,* and *HCN4*.

One mechanism of how regulation of developmentally coordinated groups of genes is achieved is through the expression of small, noncoding RNAs known as **microRNAs**, each of which regulates the expression of multiple target genes. Another is through modifications in **chromatin**, the DNA scaffolding that acts as a controller of gene expression. Chromatin remodeling mediated by genes or enzymes such as *BRG1, CHD7,* histone demethylases, and methyltransferases is associated with cardiac developmental defects, including septal defects, dilated cardiomyopathy, and double-outlet right ventricle.

469.2 Cardiac Looping

Daniel Bernstein and William R. Goodyer

At approximately 22-24 days, the heart tube begins to bend ventrally and toward the right (see Fig. 469.1). The heart is the first organ to escape from the bilateral symmetry of the early embryo. An asymmetric signaling program that also affects the position of the lungs, liver, spleen, and gastrointestinal tract determines the direction of cardiac looping. During gastrulation, before organ formation begins, asymmetric expression of *SHH* and nodal (a member of the transforming growth factor beta [TGF-β] family) are directed in the lateral

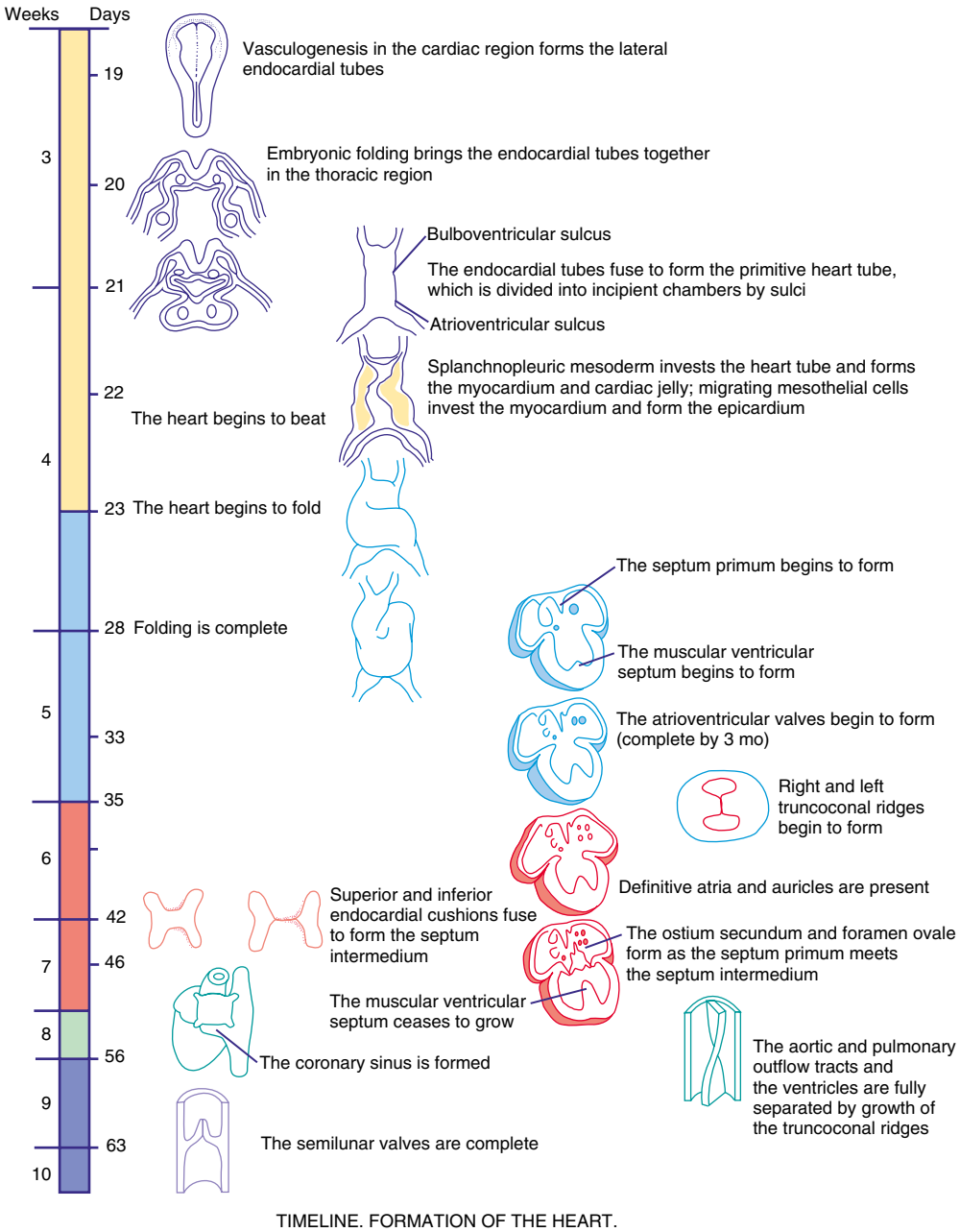

Fig. 469.1 Timeline of cardiac morphogenesis. *(From Larsen WJ. Essentials of Human Embryology. New York: Churchill Livingstone; 1998.)*

mesoderm. These directionality signals set up a concentration gradient between the right and left sides of the embryo in the expression of critical signaling molecules. This asymmetric signaling is then amplified and propagated through the transcription factor gene (*PITX2*), which is expressed on the left side of the early heart tube, *LEFTY1* and *left-right Dynein* (*LRD*). Interestingly, mice in which *LRD* has been inactivated display random left-right (L-R) orientation of the heart and abdominal viscera, with 50% of their hearts looping to the right and 50% looping to the left. Other potential mechanisms of cardiac looping include differential growth rates for myocytes on the convex versus the concave surface of the curve, differential rates of programmed cell death (apoptosis), and mechanical forces generated within myocardial cells at the inner and outer edges of the bending heart tube through their actin cytoskeleton.

Looping brings the future left ventricle leftward and in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). This pattern of development explains the relatively common occurrence of the cardiac anomalies **double-outlet right ventricle** and **double-inlet left ventricle** and the extreme rarity of double-outlet left ventricle and double-inlet right ventricle (see Chapter 479.5). When cardiac looping is abnormal **(situs inversus**, **heterotaxia)**, the incidence of serious cardiac malformations is high, and there are usually associated abnormalities in the L-R patterning of the lungs and abdominal viscera, including absence of the spleen **(asplenia)** or multiple small spleens **(polysplenia)**.

469.3 Cardiac Septation

Daniel Bernstein and William R. Goodyer

When looping is complete, the external appearance of the heart is like that of a mature heart; internally, the structure resembles a single continuous tube, although it now has several bulges resulting in the appearance of primitive chambers. The common atrium (comprising both right and left atria) is connected to the primitive ventricle (future

left ventricle) via the atrioventricular canal. The primitive ventricle is connected to the *bulbus cordis* (future right ventricle) via the *bulboventricular foramen*. The distal portion of the bulbus cordis is connected to the *truncus arteriosus* via an outlet segment (the *conus*).

The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly (acellular ECM secreted by the myocardium). Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the *endocardial cushions,* at both the atrioventricular and conotruncal junctions (see Fig. 469.1). These cushions consist of protrusions of ECM (cardiac jelly), which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells (endothelial-mesenchymal transformation) that will form part of the atrioventricular valves. The endocardium, secondary heart field, and neural crest all contribute to the formation of the valve leaflets. Besides direct contribution to valve tissue, these progenitor cells also interact with each other and with other cells in the heart to orchestrate cardiac valve development.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue is derived from the ventricular myocardium in a process involving undermining of the ventricular walls. Because this process occurs asymmetrically, the tricuspid valve annulus sits closer to the apex of the heart than the mitral valve annulus. Physical separation of these two valves produces the atrioventricular septum, the absence of which is the primary common defect in patients with **atrioventricular canal defects** (see Chapter 475.5). If the process of undermining is incomplete, the right atrioventricular valve may not separate normally from the ventricular myocardium, a possible cause of **Ebstein anomaly** (see Chapter 479.7).

Septation of the atria begins at around 30 days with growth of the septum primum downward toward the endocardial cushions (see Fig. 469.1). The orifice that remains is the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A second opening appears in the posterior portion of the septum primum, the ostium secundum, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ridge of the ostium secundum forms the *foramen ovale,* through which fetal blood passes from the inferior vena cava to the left atrium (see Chapter 470).

Septation of the ventricles begins at about embryonic day 25 with protrusions of endocardium in both the inlet (primitive ventricle) and outlet (bulbus cordis) segments of the heart. The inlet protrusions fuse into the bulboventricular septum and extend posteriorly toward the inferior endocardial cushion, where they give rise to the inlet and trabecular portions of the interventricular septum. **Ventricular septal defects** can occur in any portion of the developing interventricular septum (see Chapter 475.6). The outlet or conotruncal septum develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form a spiral septum that brings the future pulmonary artery into communication with the anterior and rightward right ventricle and the future aorta into communication with the posterior and leftward left ventricle. Differences in cell growth of the outlet septum lead to lengthening of the segment of smooth muscle beneath the pulmonary valve (conus), a process that separates the tricuspid and pulmonary valves. In contrast, disappearance of the segment beneath the aortic valve leads to fibrous continuity of the mitral and aortic valves. Within the lumen of distal outflow tract, local tissue swellings *(truncal cushions)* arise and are later populated by mesenchymal cells originating from the neural crest, participating in the formation of the semilunar (pulmonary and aortic) valves. Defects in these processes are responsible for **conotruncal** and **aortic arch defects** (truncus arteriosus, tetralogy of Fallot, pulmonary atresia, double-outlet right ventricle, interrupted aortic arch), a group of cardiac anomalies often associated with deletions of the **DiGeorge** critical region of **chromosome 22q11** (see Chapters 472 and 473). The transcription factor gene *(TBX1)* has been implicated as a candidate gene, which may be responsible for DiGeorge syndrome. Several genes have been implicated in valve formation, including *PTPN11,* which encodes the tyrosine phosphatase SHP-2, and when present in a mutated form, is one of the genes responsible for **Noonan syndrome**, associated with pulmonary valve stenosis, and *NOTCH1,* a regulator of cell differentiation associated with aortic valve disease.

469.4 Aortic Arch Development

Daniel Bernstein and William R. Goodyer

The aortic arch, head and neck vessels, proximal pulmonary arteries, and ductus arteriosus develop from the aortic sac, arterial arches, and dorsal aortae. When the straight heart tube develops, the distal outflow portion bifurcates into the right and left first aortic arches, which join the paired dorsal aortae (Fig. 469.2). The dorsal aortae will fuse to form the descending aorta. The proximal aorta from the aortic valve to the left carotid artery arises from the aortic sac. The first and second arches largely regress by about 22 days, with the first aortic arch giving rise to the maxillary artery and the second to the stapedial and hyoid arteries. The third arches participate in the formation of the innominate artery and the common and internal carotid arteries. The right fourth arch gives rise to the innominate and right subclavian arteries, and the left fourth arch participates in formation of the segment of the aortic arch between the left carotid artery and the ductus arteriosus. The fifth arch does not persist as a major structure in the mature circulation. The sixth arches join the more distal pulmonary arteries, with the right sixth arch giving rise to a portion of the proximal right pulmonary artery and the left sixth arch to the proximal left pulmonary artery and to the ductus arteriosus. The aortic arch between the ductus arteriosus and left subclavian artery is derived from the left-sided dorsal aorta, whereas the aortic arch distal to the left subclavian artery is derived from the fused right and left dorsal aortae. Abnormalities in development of the paired aortic arches are responsible for **right aortic arch**, **double aortic arch**, and **vascular rings** (see Chapter 481.1).

469.5 Cardiac Differentiation

Daniel Bernstein and William R. Goodyer

The process by which the totipotential cells of the early embryo become committed to specific cell lineages is termed *differentiation*. Precardiac mesodermal cells differentiate into mature cardiac muscle cells with an appropriate complement of cardiac-specific contractile elements, regulatory proteins, receptors, and ion channels. Expression of the contractile protein myosin occurs at an early stage of cardiac development, even before fusion of the bilateral heart primordia. Differentiation in these early mesodermal cells is regulated by signals from the anterior endoderm, a process known as *induction*. Several putative early signaling molecules include fibroblast growth factor, activin, and insulin. Signaling molecules interact with receptors on the cell surface; these receptors activate second messengers, which in turn activate specific nuclear transcription factor genes (*GATA-4, MEF2, NKX, bHLH,* and retinoic acid receptor family) that induce the expression of specific gene products to regulate cardiac differentiation. Some of the primary disorders of cardiac muscle, the **cardiomyopathies**, may be related to defects in some of these signaling molecules (see Chapter 488).

Developmental processes are chamber specific. Early in development, ventricular myocytes express both ventricular and atrial isoforms of several proteins, such as atrial natriuretic peptide (ANP) and myosin light chain (MLC). Mature ventricular myocytes do not express ANP and express only a ventricular-specific MLC 2v isoform, whereas mature atrial myocytes express ANP and an atrial-specific MLC 2a isoform. Heart failure (see Chapter 491), volume overload (see Chapters 475 and 477), and pressure overload hypertrophy (see Chapter 476)

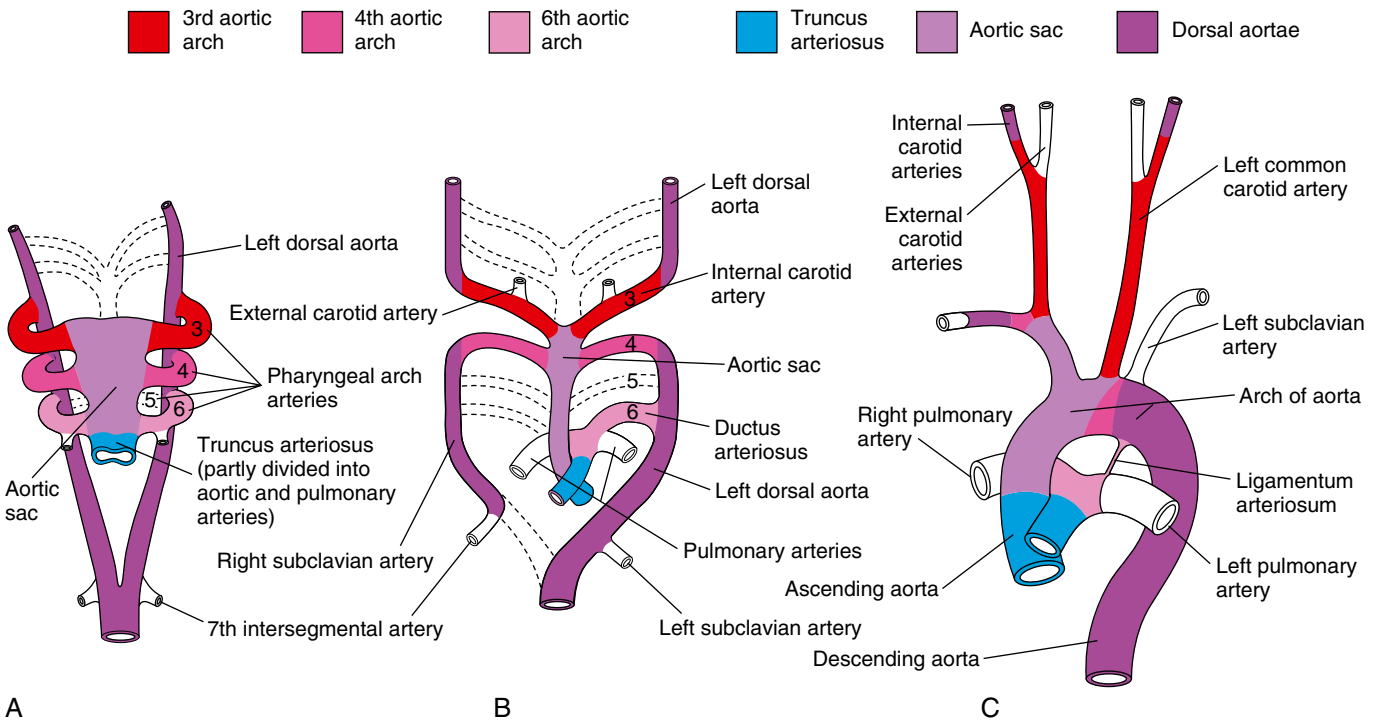

Fig. 469.2 Schematic drawings illustrating the changes that result during transformation of the truncus arteriosus, aortic sac, aortic arches, and dorsal aortae into the adult arterial pattern. The vessels that are *not* shaded or colored are not derived from these structures. **A,** Aortic arches at 6 weeks; by this stage, the first two pairs of aortic arches have largely disappeared. **B,** Aortic arches at 7 weeks; the parts of the dorsal aortae and aortic arches that normally disappear are indicated by *broken lines*. **C,** Arterial vessels of 6-mo-old infant. *(From Moore KL, Persaud TVN, Torchia M. The Developing Human. Philadelphia: Elsevier; 2007.)*

are associated with a recapitulation of fetal cell phenotypes in which mature myocytes re-express fetal proteins. Because different isoforms have different contractile behavior (fast vs slow activation, high vs low adenosine triphosphatase activity), expression of different isoforms may have important functional consequences.

469.6 Developmental Changes in Cardiac Function

Daniel Bernstein and William R. Goodyer

During development, the composition of the myocardium undergoes profound changes that result in an increase in the number and size of myocytes. During prenatal life, this process involves myocyte division **(hyperplasia)**, whereas after the first few postnatal weeks, subsequent cardiac growth occurs mostly by an increase in myocyte size **(hypertrophy)**. The myocytes themselves change shape from round to cylindrical, the proportion of myofibrils (which contain the contractile apparatus) increases, and the myofibrils become more regular in their orientation.

The *plasma membrane* (known as the *sarcolemma* in myocytes) is the location of the ion channels and transmembrane receptors that regulate the exchange of chemical information from the cell surface to the cell interior. Ion fluxes through these channels control the processes of depolarization and repolarization. Developmental changes have been described for the sodium-potassium pump, the sodium-hydrogen exchanger, and voltage-dependent calcium channels. As the myocyte matures, extensions of the sarcolemma develop toward the interior of the cell (the T-tubule system), which dramatically increases its surface area and enhances rapid activation of the myocyte. Regulation of the membrane's α- and β-adrenergic receptors with development enhances the ability of the sympathetic nervous system to control cardiac function as the heart matures.

The *sarcoplasmic reticulum* (SR), a series of tubules surrounding the myofibrils, is the principal mediator of the intracellular calcium concentration. Calcium release to the myofibrils for initiation of contraction is mediated by the ryanodine receptor (RYR), and calcium reuptake for initiation of relaxation is mediated by the sarcoplasmic reticulum calcium ATPase (SERCA). This SR calcium transport system is less well developed in immature hearts, which thus depend more on transport of calcium from outside the cell for contraction. In a mature heart, the majority of the calcium required for contraction comes from within the cardiomyocyte via the SR. This developmental phenomenon may explain the sensitivity of the infant heart to sarcolemmal calcium channel blockers such as verapamil, which can result in a marked depression in contractility (see Chapter 484).

The major contractile proteins (myosin, actin, tropomyosin, and troponin) are organized into the functional unit of cardiac contraction, the *sarcomere*. Each has several isoforms that are expressed differentially by location (atrium vs ventricle) and by developmental stage (embryo, fetus, newborn, adult).

Changes in myocardial structure and myocyte biochemistry result in easily quantifiable differences in cardiac function with development. Fetal cardiac function is less responsive to changes in preload (filling volume). Thus the most effective means of increasing cardiac output in the fetus is through increasing the heart rate. After birth and with further maturation, preload and afterload play an increasing role in regulating cardiac function. The rate of cardiac relaxation is also developmentally regulated. The decreased ability of the immature SR calcium pump (SERCA) to remove calcium from the contractile apparatus is manifested as a decreased ability of the fetal heart to enhance relaxation in response to sympathetic stimulation.

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Chapter 470

The Fetal to Neonatal Circulatory Transition

Daniel Bernstein

470.1 The Fetal Circulation

Daniel Bernstein

The transition from the fetal to the postnatal circulation represents one of the most dramatic circulatory adaptations at any time of life. In the fetal circulation, the right and left ventricles exist in a parallel circuit, as opposed to the series circuit of the newborn or adult (Fig. 470.1A). In the fetus, the placenta provides for gas and metabolite exchange. Because the lungs do not provide gas exchange, blood is diverted away from the pulmonary circulation, which is vasoconstricted. Three cardiovascular structures unique to the fetus are important for maintaining this parallel circulation: the *ductus venosus, foramen ovale,* and *ductus arteriosus.*

The placenta is not as efficient an oxygen-exchange organ as the lungs, so that umbilical venous partial pressure of oxygen (Po_2), the highest O_2 level provided to the fetus, is only 30-35 mm Hg. Approximately 50% of the umbilical venous blood enters the hepatic circulation, whereas the rest bypasses the liver and joins the inferior vena cava (IVC) via the ductus venosus, where it partially mixes with poorly oxygenated IVC blood derived from the lower part of the fetal body. This combined lower body plus umbilical venous blood flow (Po_2 of 26-28 mm Hg) enters the right atrium and is preferentially directed by a flap of tissue at the right atrium–IVC junction, the eustachian valve, across the foramen ovale to the left atrium (see Fig. 470.1B). This is the major source of left ventricular (LV) blood flow in the fetus, because pulmonary venous return from the vasoconstricted lungs is minimal. LV blood is then ejected into the ascending aorta, where it supplies predominantly the fetal upper body and brain.

Fetal superior vena cava (SVC) blood, which is considerably less oxygenated (Po_2 of 12-14 mm Hg) than IVC blood, enters the right atrium and preferentially flows across the tricuspid valve, rather than the foramen ovale, into the right ventricle. From the right ventricle, this blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular (RV) outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right to left through the ductus arteriosus into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the two umbilical arteries. Thus the upper part of the fetal body (including the coronary and cerebral arteries and those to the upper extremities) is perfused exclusively from the left ventricle with blood that has a slightly higher Po_2 than the blood perfusing the lower part of the fetal body, which is derived mostly from the right ventricle. Only a small volume of blood from the ascending aorta (10% of fetal cardiac output) flows all the way around the aortic arch (aortic isthmus) to the descending aorta.

The **total fetal cardiac output**—the combined output of both the left and right ventricles—is approximately 450 mL/kg/min. Approximately 65% of descending aortic blood flow returns to the placenta; the remaining 35% perfuses the fetal organs and tissues. In the human fetus, RV output is approximately 1.3 times LV flow. Thus during fetal life the right ventricle is not only pumping against the higher systemic blood pressure but also performing slightly greater volume work than the left ventricle. This results in the RV wall being as thick (hypertrophied) as the LV wall during fetal and immediate neonatal life, explaining the unique features of the neonatal electrocardiogram (showing what would be read as *right ventricular hypertrophy* in an adult).

Blood flow is believed to be an important determinant of growth of fetal cardiac chambers, valves, and blood vessels. Thus in the presence of a narrowing (stenosis) of an upstream structure such as the mitral valve, flow downstream into the left ventricle is limited and LV growth may be compromised, which may be one of the mechanisms of **hypoplastic left heart syndrome** (HLHS; see Chapter 480.10). Similarly, stenosis of a downstream structure such as the aortic valve can also disrupt flow into the LV and contribute to HLHS. Fetal cardiac interventional treatments, currently experimental, are aimed at opening stenotic aortic valves in mid-gestation fetuses and allowing more normal LV growth. However, the outcome of these procedures does not enhance LV growth in all patients, suggesting that in the majority of cases of HLHS there is a different mechanism, suspected to be a defect in the LV cardiomyocytes themselves (i.e., a cell-autonomous defect).

470.2 The Transitional Circulation

Daniel Bernstein

At birth, mechanical expansion of the lungs and an increase in arterial Po_2 result in a rapid decrease in pulmonary vascular resistance (PVR). Concomitantly, removal of the low-resistance placental circulation leads to an increase in systemic vascular resistance (SVR). The output from the right ventricle now flows entirely into the pulmonary circulation, and because PVR becomes lower than SVR, the shunt through the ductus arteriosus reverses and becomes left to right. Over several days the high arterial Po_2 constricts and eventually closes the ductus arteriosus, which eventually becomes the ligamentum arteriosum. The increased volume of pulmonary blood flow returning to the left atrium from the lungs increases left atrial volume and pressure sufficiently to close the flap of the foramen ovale functionally, although the foramen may remain patent on probing with a catheter for several years. A patent foramen ovale can be a source of embolic stroke in later life.

Removal of the placenta from the circulation also results in closure of the ductus venosus. The left ventricle is now coupled to the high-resistance systemic circulation, and its wall thickness and mass begin to increase. In contrast, the right ventricle is now coupled to the low-resistance pulmonary circulation, and its wall thickness and mass decrease. The left ventricle, which in the fetus pumped blood only to the upper part of the body and brain, must now deliver the entire systemic cardiac output (approximately 350 mL/kg/min), an almost 200% increase in output. This marked increase in LV performance is achieved through a combination of hormonal and metabolic signals, including an increase in the level of circulating catecholamines and in the density of myocardial β-adrenergic receptors, through which catecholamines have their effect.

When superimposed on these dramatic physiologic changes, congenital structural cardiac defects often impede this smooth transition and greatly increase the burden on the newborn myocardium. Importantly, because the ductus arteriosus and foramen ovale do not close completely at birth, they can provide a lifesaving pathway for blood to bypass a congenital defect (the patent ductus arteriosus in tetralogy of Fallot, pulmonary atresia, coarctation of aorta or HLHS; the foramen ovale in transposition of the great vessels). Alternatively, persistent fetal pathways can present an additional stress to the circulation (patent ductus arteriosus in the premature infant). Therapeutic agents can be used to either maintain these fetal pathways open (e.g., *prostaglandin E_1*) or hasten their closure (e.g., *indomethacin*). This pharmacology explains why indomethacin and similar drugs are contraindicated or used with extreme caution during the third trimester.

470.3 The Neonatal Circulation

Daniel Bernstein

At birth, the fetal circulation must immediately adapt to extrauterine life as gas exchange is transferred from the placenta to the lungs (see

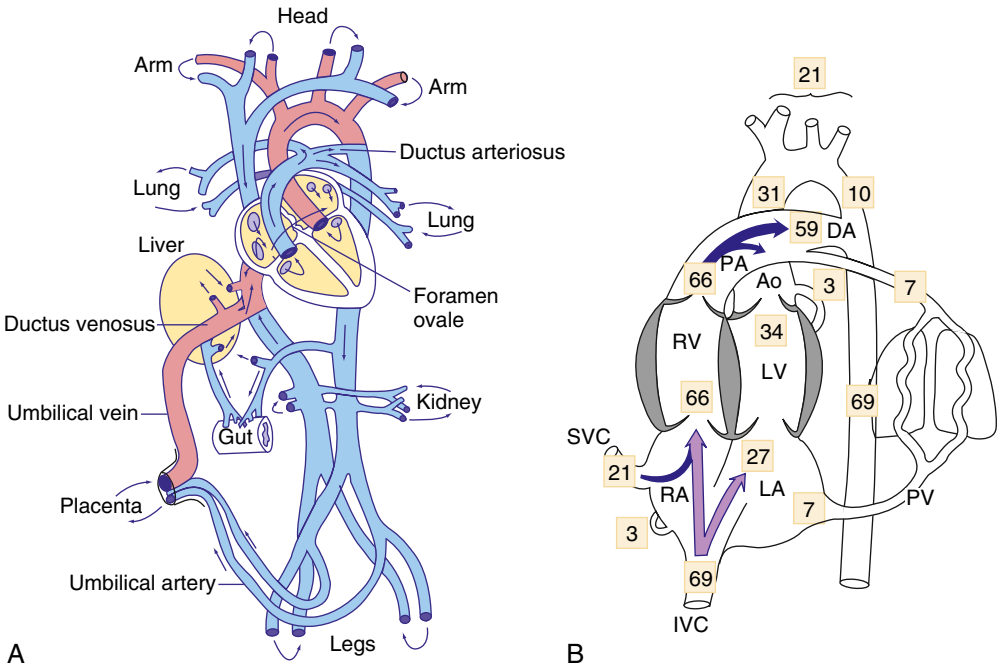

Fig. 470.1 A, The human circulation before birth (partly after Dawes). *Red* indicates more highly oxygenated blood, and *arrows* indicate the direction of flow. More highly oxygenated blood from the placenta passes through the foramen ovale from the right to the left atrium, thus bypassing the lungs. B, Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures are those obtained from studies of late-gestation fetal lambs. Ao, Aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. *(From Rudolph AM. Congenital Diseases of the Heart. Chicago: Year Book; 1974.)*

Chapter 124). Some of these changes are virtually instantaneous with the first breath, whereas others develop over hours or weeks. With the onset of breathing and lung ventilation, pulmonary vascular resistance is greatly decreased because of both active (i.e., Po_2-metabolic-related) and passive (i.e., mechanical stretch-related) pulmonary vasodilation. In a normal neonate, closure of the ductus arteriosus and the fall in PVR decreases pulmonary arterial and RV pressures. The largest decline in PVR from the high fetal levels to the lower "adult" levels in the human infant usually occurs within 2-3 days, but may be prolonged for ≥7 days after birth. However, over the next several weeks of life, PVR continues to decrease further, now secondary to physical remodeling of the pulmonary vasculature, including thinning of vascular smooth muscle and recruitment of new vessels. This decrease in PVR significantly influences the timing of the clinical appearance of many congenital heart lesions dependent on the relative levels of SVR and PVR. For example, the left-to-right shunt through a large ventricular septal defect (VSD) may be minimal in the first week after birth, when PVR is still high. As PVR decreases in the next 1-2 weeks, the volume of the left-to-right shunt through the VSD increases and eventually leads to the signs and symptoms of heart failure.

There are several significant differences between the neonatal circulation and that of older infants: (1) right-to-left or left-to-right shunting may persist across the patent foramen ovale; (2) in the presence of cardiopulmonary disease, continued patency of the ductus arteriosus may allow left-to-right, right-to-left, or bidirectional shunting; (3) the neonatal pulmonary vasculature constricts more vigorously in response to hypoxemia, hypercapnia, and acidosis; (4) the wall thickness and muscle mass of the neonatal left and right ventricles are almost equal; and (5) newborn infants at rest have a relatively high oxygen consumption, associated with a relatively high cardiac output. The newborn cardiac output, indexed to body weight (200 mL/kg/min), falls in the first 2 months of life to approximately 150 mL/kg/min and then more gradually to the normal adult cardiac output of 75 mL/kg/min. Although fetal hemoglobin is beneficial to delivery of oxygen in the low-Po_2 fetal circulation, the high percentage of fetal hemoglobin present in the newborn may actually interfere with delivery of oxygen to tissues in the high-systemic Po_2 neonatal circulation, and therefore adult hemoglobin production begins immediately (see Chapter 124).

The foramen ovale is usually functionally closed by the third month of life, although it is possible to pass a catheter through the overlapping flaps in a large percentage of children and in 15–25% of adults. Functional closure of the ductus arteriosus is usually complete by 10-15 hours of postnatal age in a normal neonate, although the ductus may remain patent much longer in the presence of congenital heart disease, especially when associated with cyanosis. In premature newborn infants, a systolic murmur with late accentuation or a continuous murmur may be audible beneath the left clavicle, and in the context of respiratory distress syndrome, the presence of a patent ductus arteriosus should be suspected (see Chapter 126.1).

The normal ductus arteriosus differs morphologically from the adjoining aorta and pulmonary artery in that the ductus has a significant amount of circularly arranged smooth muscle in its medial layer. During fetal life, patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E_2. In a full-term neonate, oxygen is the most important factor controlling ductal closure. When the Po_2 of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall begins to constrict. The effects of oxygen on ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis. Gestational age also appears to play an important role; the ductus of a premature infant is less responsive to oxygen, even though its musculature is well developed.

470.4 Persistent Pulmonary Hypertension of the Neonate (Persistence of Fetal Circulatory Pathways)

See Chapter 130.

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Section 2

Evaluation of the Cardiovascular System and the Child with a Heart Murmur

Chapter 471

History and Physical Examination in Cardiac Evaluation

Daniel Bernstein

One of the most common reasons for cardiac evaluation in young children is the heart murmur; **innocent or functional murmurs (Still murmurs)** may be heard in up to 30% of patients at some time during childhood. Functional murmurs are usually accentuated by fever and first noticed during a visit for an intercurrent illness. Thus the general pediatrician must be able to distinguish those murmurs that are functional from those that are potentially pathologic and refer patients with pathologic-sounding murmurs or murmurs of uncertain nature for evaluation by a pediatric cardiologist.

Patients may require further laboratory evaluation (e.g., electrocardiogram and echocardiogram), or the family may be reassured that no significant problem exists. Although the ready availability of echocardiography may entice the clinician to skip a good history and physical exam, an initial evaluation by a skilled cardiologist is preferred for several reasons: (1) a cardiac examination allows the cardiologist to guide the echocardiographic evaluation toward confirming or eliminating specific diagnoses, thereby increasing its accuracy; (2) because most childhood murmurs are innocent, evaluation by a pediatric cardiologist can eliminate unnecessary and expensive laboratory tests; and (3) the cardiologist's knowledge and experience are important in reassuring the patient's family and preventing unnecessary, and all too common, restrictions on healthy physical activity. An experienced pediatric cardiologist can differentiate an innocent murmur from serious congenital heart disease by history and physical examination alone with high sensitivity and specificity.

HISTORY

The evaluation begins with a comprehensive cardiac history because a diagnosis of a functional murmur can only be made in the absence of any concerning symptoms, signs, or family history. A comprehensive cardiac history starts with details of the perinatal period, including the presence of cyanosis, respiratory distress, or prematurity. **Maternal complications** such as gestational diabetes, teratogenic medications, infections, systemic lupus erythematosus, or substance misuse can be associated with cardiac problems. If cardiac symptoms began during infancy, the timing of the initial symptoms should be noted to provide important clues about the specific cardiac condition.

Many of the symptoms of **heart failure** in infants and children are age specific. In infants, feeding difficulties are common. Inquiry should be made about the frequency of feeding and either the volume of each feeding or the time spent on each breast. An infant with heart failure often takes less volume per feeding and becomes dyspneic or diaphoretic while nursing. After falling asleep exhausted, the baby, inadequately fed, will awaken for the next feeding after a brief time. This cycle continues around the clock and must be carefully differentiated from colic or other feeding disorders. Additional symptoms and signs include those of respiratory distress: rapid breathing, nasal flaring, cyanosis, and chest retractions. In older children, heart failure may be manifested as exercise intolerance, difficulty keeping up with peers during sports or the need for a nap after coming home from school, poor growth, or chronic abdominal complaints. Eliciting a history of fatigue in an older child requires questions about age-specific activities, including stair climbing, walking, bicycle riding, physical education class, and competitive sports; information should be obtained regarding more severe manifestations such as orthopnea and nocturnal dyspnea.

Parents often overlook their baby's **cyanosis** at rest; it may be mistaken for a normal individual variation in color. Cyanosis during crying or exercise, however, is more often noted as abnormal by observant parents. Many infants and toddlers turn "blue around the lips" when crying vigorously or during breath-holding spells; this condition must be carefully differentiated from **cyanotic heart disease** by inquiring about inciting factors, the length of episodes, and whether the tongue and mucous membranes also appear cyanotic. Newborns often have cyanosis of their extremities **(acrocyanosis)** when undressed and cold; this response to cold must be carefully differentiated from true cyanosis, where the mucous membranes are also blue.

Chest pain is an unusual manifestation of cardiac disease in pediatric patients, although it is a frequent cause for referral to a pediatric cardiologist, especially in adolescents. Nonetheless, a careful history, physical examination, and, if indicated, laboratory or imaging tests will assist in identifying the cause of chest pain (Table 471.1). For patients with some forms of repaired congenital heart disease (CHD), for example, those with surgery on the aortic root or those with a history of Kawasaki disease (see Chapter 493.1), chest pain should be evaluated carefully for a coronary etiology.

Cardiac disease may be a manifestation of a known congenital malformation syndrome with typical physical findings (Table 471.2) or a manifestation of a generalized disorder affecting the heart and other organ systems (Table 471.3). **Extracardiac malformations** may be noted in 20–45% of infants with CHD. Between 5% and 10% of patients have a known chromosomal abnormality. Specific gene or whole exome sequencing can enhance the diagnostic approach to CHD (Fig. 471.1).

A careful family history may also reveal early (at age <50 years) coronary artery disease or stroke (suggestive of familial hypercholesterolemia or thrombophilia), sudden death (suggestive of cardiomyopathy or familial arrhythmic disorder), generalized muscle disease (suggestive of one of the muscular dystrophies, dermatomyositis, or familial or metabolic cardiomyopathy), or first-degree relatives with CHD.

GENERAL PHYSICAL EXAMINATION

In the evaluation of a child with a heart murmur, a general physical examination is always performed, with specific attention directed toward the presence of cyanosis, abnormalities in growth, chest wall abnormalities, and any evidence of respiratory distress. Although the murmur may be the most prominent part of the overall examination, any murmur must be placed in context of other physical findings. Associated findings such as quality of the pulses, presence of a ventricular heave or thrill, or splitting of the second heart sound provide important clues to a specific cardiac diagnosis.

Accurate measurement of height and weight and plotting on a standard growth chart are important because both cardiac failure and chronic cyanosis can result in failure to thrive. Growth failure is manifested predominantly by poor weight gain; if length and especially head circumference is also affected, additional congenital malformations or metabolic disorders should be suspected.

Mild cyanosis may be too subtle for early detection, and clubbing of the fingers and toes is not usually manifested until late in the first year of life, even in the presence of severe arterial oxygen desaturation. Cyanosis is best observed over the nail beds, lips, tongue, and mucous membranes. Delayed recognition of cyanosis in infants with darker skin color

Table 471.1 Differential Diagnosis of Chest Pain in Pediatric Patients

MUSCULOSKELETAL (COMMON)
Trauma (accidental, abuse)
Exercise, overuse injury (strain, bursitis)
Costochondritis
Tietze syndrome
Herpes zoster (cutaneous or without rash)
Pleurodynia
Fibrositis
Slipping rib
Rib fracture
Precordial catch
Sickle cell anemia vasoocclusive crisis
Osteomyelitis (rare)
Primary or metastatic tumor (rare)
Fibromyalgia
Nerve entrapment, radiculopathy
PULMONARY (COMMON)
Pneumonia
Pleurisy
Pleurodynia
Asthma
Chronic cough
Pneumothorax
Infarction (sickle cell anemia)
Foreign body
Embolism (rare)
Pulmonary hypertension (rare)
Tumor (rare)
Bronchiectasis
GASTROINTESTINAL (LESS COMMON)
Esophagitis (gastroesophageal reflux, infectious, pill)
Esophageal foreign body
Esophageal spasm
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh-Curtis syndrome)
Peptic ulcer disease
Pancreatitis
Splenic rupture
CARDIAC (LESS COMMON)
Pericarditis
Postpericardiotomy syndrome
Endocarditis
Myocarditis
Cardiomyopathy
Mitral valve prolapse
Aortic or subaortic stenosis
Arrhythmias (supraventricular, ventricular, tachycardias)
Marfan syndrome (dissecting aortic aneurysm)
Kawasaki disease
Cocaine, sympathomimetic ingestion
Ischemia (familial hypercholesterolemia, anomalous coronary artery, post-repair of congenital heart disease involving reimplantation of the coronary arteries [e.g., d-transposition of the great arteries])
Takotsubo cardiomyopathy (primary or secondary)
IDIOPATHIC (COMMON)
Anxiety, hyperventilation
Panic disorder
OTHER (LESS COMMON)
Spinal cord or nerve root compression
Breast-related pathologic condition (mastalgia)
Castleman disease (lymph node neoplasm)

can lead to delayed treatment and poorer outcomes. Careful observation of the color of the tongue, mucous membranes, and nail beds, where cyanosis is most noticeable, is critical in recognizing cyanosis in these patients. Confirmation with pulse oximetry is easily performed.

Differential cyanosis, manifested as blue lower extremities and pink upper extremities (usually the right arm), is seen with right-to-left shunting across a ductus arteriosus in the presence of coarctation or an interrupted aortic arch. Circumoral cyanosis or blueness around the forehead may be the result of prominent venous plexuses in these areas, rather than decreased arterial oxygen saturation. The extremities of infants often turn blue when the infant is unwrapped and cold (acrocyanosis), and this condition can be distinguished from central cyanosis by examination of the tongue and mucous membranes.

Heart failure in infants and children usually results in some degree of hepatomegaly and occasionally splenomegaly. The sites of **peripheral edema** are age dependent. In infants, edema is usually seen around the eyes and over the flanks, especially on initially waking. Older children and teenagers manifest both periorbital edema and pedal edema. An initial complaint in these older patients may be that their clothes are now too tight.

The **heart rate** of newborn infants is rapid and subject to wide fluctuations (Table 471.4). The average rate ranges from 120 to 140 beats/min and may increase to 170+ beats/min during crying and activity or drop to 70-90 beats/min during sleep. As the child grows older, the average pulse rate decreases and may be as low as 40 beats/min at rest in very athletic adolescents. Persistent **tachycardia** (>200 beats/min in neonates, 150 beats/min in infants, or 120 beats/min in older children), bradycardia, or an irregular heartbeat other than sinus arrhythmia requires investigation to exclude pathologic arrhythmias (see Chapter 484). **Sinus arrhythmia** can usually be distinguished by the rhythmic nature of the heart rate variations, occurring in concert with the respiratory cycle, with a P wave before every QRS complex, and a normal p-wave axis.

Careful evaluation of the character of the **pulses** is an important early step in the physical diagnosis of CHD. A wide pulse pressure with bounding pulses may suggest an aortic runoff lesion such as patent ductus arteriosus (PDA), aortic insufficiency, an arteriovenous communication, or increased cardiac output secondary to anemia, anxiety, or conditions associated with increased catecholamine or thyroid hormone secretion. The presence of diminished pulses in all extremities is associated with pericardial tamponade, left ventricular outflow obstruction, or cardiomyopathy. The radial and femoral pulses should always be palpated simultaneously. Normally, the femoral pulse should be appreciated immediately before the radial pulse. In infants with coarctation of the aorta, the femoral pulses may be decreased. However, in older children with coarctation of the aorta, blood flow to the descending aorta may channel through collateral vessels and results in the femoral pulse being palpable but delayed until after the radial pulse **(radial-femoral delay)**.

Blood pressure (BP) should be measured in either leg and in the right arm to be certain that coarctation of the aorta is not overlooked. Palpation of the femoral or dorsalis pedis pulse, or both, is not reliable alone to exclude coarctation because collaterals may have developed. Most commonly, BP is measured using an automated oscillatory device, but it is often necessary for the physician to manually recheck BP by auscultation. In older children, a cuff that covers approximately two thirds of the upper part of the arm or leg should be used for BP measurement. A cuff that is too small results in falsely high readings, whereas a cuff that is too large records slightly decreased BP. Pediatric clinical facilities should be equipped with 3-, 5-, 7-, 12-, and 18-cm cuffs to accommodate the large spectrum of pediatric patient sizes. When auscultating blood pressure directly, the first Korotkoff sounds indicate systolic pressure. As cuff pressure is slowly decreased, the sounds usually become muffled before they disappear. Diastolic pressure may be recorded when the sounds become muffled (preferred) or when they disappear altogether; the former is usually slightly higher and the latter slightly lower than true diastolic pressure. For lower-extremity BP determination, the stethoscope is placed over the popliteal artery. Typically, the BP recorded in the legs with the cuff technique is approximately 10 mm Hg higher than that in the arms. In infants, BP can be determined by auscultation or palpation.

BP varies with the age of the child and is closely correlated to height and weight. Significant increases occur during adolescence, and many temporary variations take place before the more stable levels of adult life are attained. Exercise, excitement, coughing, crying, and struggling may raise the systolic BP of infants and children as much as 40-50 mm Hg greater than their usual levels. Variability in BP in children of

Table 471.2 Congenital Malformation Syndromes Associated with Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat-eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, TOF, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous, VSD
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous
Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD, TOF
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
Deletion 1p36	ASD, VSD, PDA, TOF, cardiomyopathy
Deletion/duplication 1q21.1	ASD, VSD, PS
Deletion 17q11 (William syndrome)	Supravalvar AS, branch PS
Deletion 11q 24-25 (Jacobsen syndrome)	VSD, left sided lesions
SYNDROME COMPLEXES	
CHARGE association (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation, *g*enital, and *e*ar anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (*c*ardiac defects, *a*bnormal facies, *t*hymic aplasia, *c*left palate, *h*ypocalcemia, and deletion 22q11)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (vertebral, *a*nal, *t*racheo*e*sophageal, *r*adial, and *r*enal anomalies)	VSD, TOF, ASD, PDA
FAVS (*f*acio*a*uriculo*v*ertebral *s*pectrum)	TOF, VSD
CHILD (congenital *h*emidysplasia with *i*chthyosiform erythroderma, *l*imb *d*efects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (*p*osterior brain fossa anomalies, facial *h*emangiomas, *a*rterial anomalies, *c*ardiac anomalies and aortic coarctation, *e*ye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD

Continued

Table 471.2 Congenital Malformation Syndromes Associated with Congenital Heart Disease—cont'd

SYNDROME	FEATURES
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
De Lange syndrome	VSD
Ellis–van Creveld syndrome	Single atrium, VSD
Holt-Oram syndrome	ASD, VSD, first-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Primary ciliary dyskinesia	Heterotaxia disorders
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA

*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.
ASD, Atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

approximately the same age and body build should be expected, and at least three serial measurements on different dates should be obtained when confirming the diagnosis of hypertension (Figs. 471.2 and 471.3).

Although of little use in infants, in cooperative older children, inspection of the **jugular venous pulse** wave provides information about central venous and right atrial pressure. The neck veins should be inspected with the patient sitting at a 90-degree angle. The external jugular vein should not be visible above the clavicles unless central venous pressure is elevated. Increased venous pressure transmitted to the internal jugular vein may appear as venous pulsations without visible distention; such pulsation is not seen in normal children reclining at an angle of 45 degrees. Because the great veins are in direct communication with the right atrium, changes in pressure and the volume of this chamber are also transmitted to the veins. The one exception occurs in superior vena cava obstruction, in which venous pulsatility is lost.

CARDIAC EXAMINATION

The heart should be examined in a systematic manner, starting with inspection and palpation. Any abnormalities on inspection and/or palpation strongly suggest a pathologic rather than a functional etiology of any heart murmur. A **precordial bulge** to the left of the sternum with or without increased precordial activity suggests cardiac enlargement, especially in younger children where the chest wall is still relatively flexible; such bulges can often best be appreciated by having the child lay supine with the examiner looking up from the child's feet. A **substernal heave** indicates the presence of right ventricular hypertrophy or enlargement, whereas an **apical heave** is noted with left ventricular hypertrophy or enlargement. An overall **hyperdynamic precordium** suggests a volume load such as that found with a large left-to-right shunt, although it may be normal in a thin patient. An overly silent precordium with a barely detectable apical impulse suggests a large pericardial effusion or severe cardiomyopathy but may be normal in an obese patient.

The relationship of the **apical impulse** to the midclavicular line is also helpful in the estimation of cardiac size: the apical impulse shifts laterally and inferiorly with enlargement of the left ventricle. Right-sided apical impulses signify dextrocardia, tension pneumothorax, or left-sided thoracic space-occupying lesions (e.g., diaphragmatic hernia).

Thrills are the palpable equivalent of murmurs and correlate with the area of maximal auscultatory intensity of the murmur. It is important to palpate the suprasternal notch and neck for aortic bruits, which may indicate the presence of aortic stenosis. Right lower sternal border and apical systolic thrills are characteristic of ventricular septal defect (VSD) and mitral insufficiency, respectively. Diastolic thrills are occasionally palpable in the presence of atrioventricular valve stenosis. The timing and localization of thrills should be carefully noted. Although the presence of a thrill is usually linked to a murmur of grade IV or greater, after a patient has had cardiac surgery, the presence of scar within the chest may eliminate the ability to feel a thrill even with a very loud murmur.

Table 471.3 Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
COVID-19	Myocarditis, multisystem inflammatory syndrome in children (MIS-C)
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence
CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta, heart failure, hypertension
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractural arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilatated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel-Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis

Continued

Table 471.3 Cardiac Manifestations of Systemic Diseases—cont'd

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (first or second degree)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Jervell and Lange-Nielsen syndrome	Prolonged Q-T interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, Multiple *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth, *s*ensorineural *d*eafness.

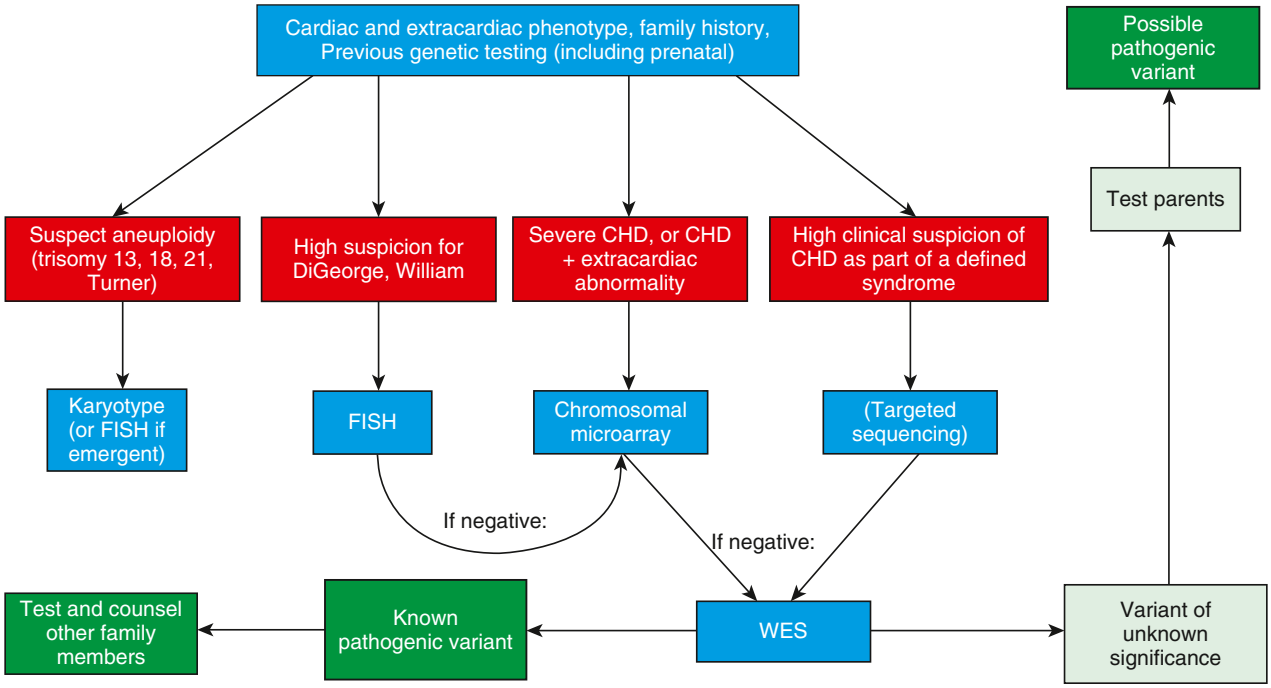

Fig. 471.1 Genetics screening algorithm for congenital heart disease (CHD) patients. FISH, Fluorescence in situ hybridization; WES, whole exome sequencing. *(From Simmons MA, Brueckner M. The genetics of congenital heart disease . . . understanding and improving long-term outcomes in congenital heart disease: a review for the general cardiologist and primary care physician. Curr Opin Pediatr. 2017;29:520–528, Fig 2.)*

Auscultation is an art that improves with practice. The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds. The physician should initially move the stethoscope across the chest, concentrating on the characteristics of the heart sounds; their variation with respiration; and the presence of clicks, rubs, or gallops. Repeat the process, concentrating on murmurs, their maximum location, and their radiation. In some CHDs, such as atrial septal defect (ASD), the murmur is nonspecific and sounds identical to many functional murmurs; it is the abnormality of the second heart sound that points to a pathologic condition. The patient should ideally be supine, lying quietly, and breathing normally. The **first heart sound** (S_1) is best heard at the apex, whereas the **second heart sound** (S_2) should be evaluated at the upper left and right sternal borders. S_1 is caused by closure of the atrioventricular valves (mitral and tricuspid) and can be either single or split. S_2 is caused by closure of the semilunar valves (aortic and pulmonary) (Fig. 471.4). During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to

Table 471.4 Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)		AVERAGE (beats/min)		UPPER LIMITS OF NORMAL (beats/min)	
Newborn	70		125		190	
1-11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; inspiration decreases pulmonary venous return, decreasing filling of the left ventricle and moving closure of the aortic valve earlier. Consequently, **splitting of the second heart sound** widens during inspiration and narrows during expiration.

S_2 can appear to be single during expiration, because we can only hear two sounds if they are separated by 20-30 msec. The presence of a normally split S_2 is strong evidence against the diagnosis of ASD, defects associated with pulmonary arterial hypertension, severe pulmonary valve stenosis, aortic and pulmonary atresia, and truncus arteriosus. Wide S_2 splitting is noted in ASD, pulmonary stenosis (where the pulmonary second sound is soft), Ebstein anomaly, total anomalous pulmonary venous return, and right bundle branch block. An accentuated pulmonic component of S_2 with narrow splitting is a sign of pulmonary hypertension. A single S_2 occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.

A **third heart sound** (S_3) is best heard with the bell at the apex in mid-diastole, during passive ventricular filling. An S_3 can be pathologic but may be normal in children, often accentuated in patients with fever and tachycardia. A **fourth heart sound** (S_4), occurring in conjunction with atrial systole and the final stages of ventricular filling, may be heard just before the S_1 in late diastole. An S_4 is always pathologic and an indication of decreased ventricular compliance, as occurs in patients with ventricular dysfunction (e.g., in dilated cardiomyopathy). An S_3 may merge with an S_4, a finding known as a **summation gallop**.

Ejection clicks, which are heard in early systole, are usually caused by a mildly to moderately stenotic aortic or pulmonary valve or to a dilated ascending aorta or pulmonary artery. They are heard so close to S_1 that they may be mistaken for a split S_1. However, ejection clicks are heard at the upper left or right sternal borders, whereas a split S_1 is heard at the lower left sternal border or apex. **Aortic** ejection clicks are best heard at the left middle to right upper sternal border and are constant in intensity. They occur in conditions where the aortic valve (mild to moderate aortic stenosis) is stenotic or the aorta is dilated (e.g., tetralogy of Fallot, truncus arteriosus). **Pulmonary** ejection clicks are associated with mild to moderate pulmonary stenosis and are best heard at the left middle to upper sternal border and vary with respiration, often disappearing with inspiration. A good place to hear ejection clicks is right over the sternum, since bone conducts high-frequency sound much better than the muscle of the intercostal spaces. A midsystolic click heard at the apex, often preceding a late systolic murmur, suggests mitral valve prolapse.

Murmurs should be described according to their intensity, pitch, timing (systolic or diastolic), variation in intensity, time to peak intensity, location of maximal intensity, and radiation to other areas. Auscultation for murmurs should be carried out starting at the upper right sternal border then moving slowly across the upper precordium, down the left and right sternal borders, and out to the apex and to the left axilla. Auscultation should also always be performed in the right axilla and over both sides of the back, as many CHD murmurs radiate to these locations. Systolic murmurs are classified as ejection, holosystolic or pansystolic, or late systolic according to the timing of the murmur in relation to S_1 and S_2. The intensity of systolic murmurs is graded from I to VI: **I**, barely audible; **II**, medium intensity; **III**, loud but no thrill; **IV**, loud with a thrill; **V**, very loud but still requiring positioning of the stethoscope at least partly on the chest; and **VI**, so loud that the murmur can be heard with the stethoscope off the chest. In patients who have undergone prior heart surgery, a murmur of grade IV or greater may be heard in the absence of a thrill because of scar tissue, which does not transmit vibrations well, within the chest.

Systolic ejection murmurs start a short time after a well-heard S_1, increase in intensity, peak, and then decrease in intensity; they usually end before S_2. In patients with severe pulmonary stenosis, however, the murmur may extend beyond the first component of S_2, thus obscuring it. **Pansystolic or holosystolic murmurs** begin simultaneously with S_1 and continue throughout systole, on occasion becoming gradually decrescendo. It is important to remember that after closure of the atrioventricular valves (S_1), a brief period occurs during which ventricular pressure increases but the semilunar valves remain closed (isovolumic contraction; see Fig. 471.4). Thus holosystolic murmurs (heard during both isovolumic contraction and the ejection phases of systole) cannot be caused by flow across the semilunar valves because these valves are closed during isovolumic contraction! Holosystolic murmurs must therefore be related to blood exiting the contracting ventricle via either an abnormal opening (VSD) or atrioventricular (mitral or tricuspid) valve insufficiency. Systolic ejection murmurs usually imply increased flow or stenosis across one of the ventricular outflow tracts (aortic or pulmonic). In infants with rapid heart rates, it is often difficult to distinguish between ejection and pansystolic murmurs. If a clear and distinct S_1 can be appreciated, the murmur is most likely ejection in nature.

A **continuous murmur** is a murmur that continues from systole into diastole and indicates continuous flow, such as in the presence of a PDA or other aortopulmonary communication. This murmur should be differentiated from a **to-and-fro murmur**, where the systolic component of the murmur ends at or before S_2 and the diastolic murmur begins after S_2 with semilunar valve closure (aortic stenosis and insufficiency; pulmonary stenosis and insufficiency). A **late systolic murmur** begins well beyond S_1 and continues until the end of systole and is usually heard after a midsystolic click in patients with mitral valve prolapse and insufficiency.

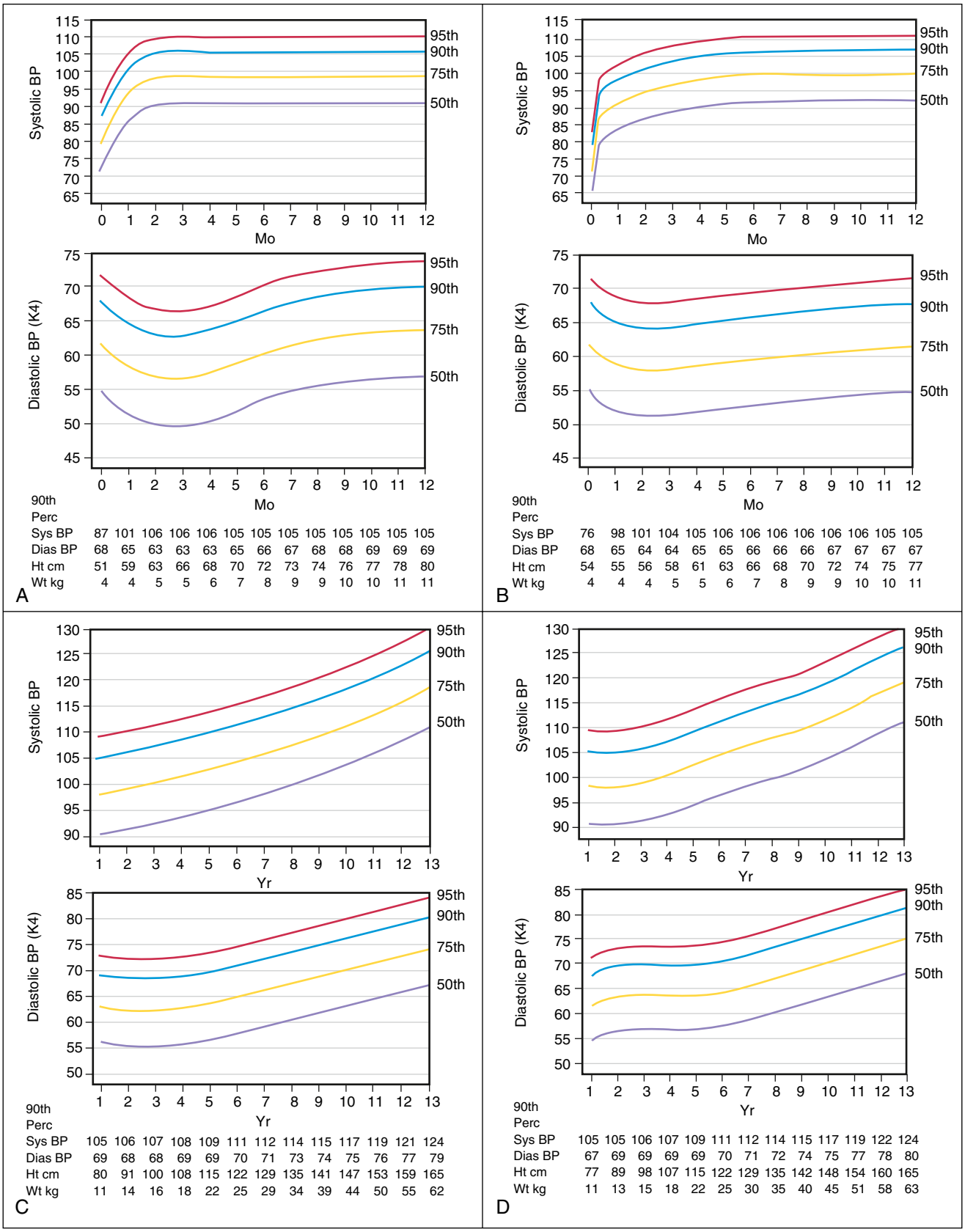

Fig. 471.2 Age-specific percentiles of blood pressure (BP) measurements: birth to 13 yr. **A,** Males from birth to 12 mo of age. **B,** Females from birth to 12 mo of age. **C,** Males 1-13 yr of age. **D,** Females 1-13 yr of age. Korotkoff phase IV (K4) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD. Pediatrics. 1987;79:1–25. Copyright 1987 by the American Academy of Pediatrics.)*

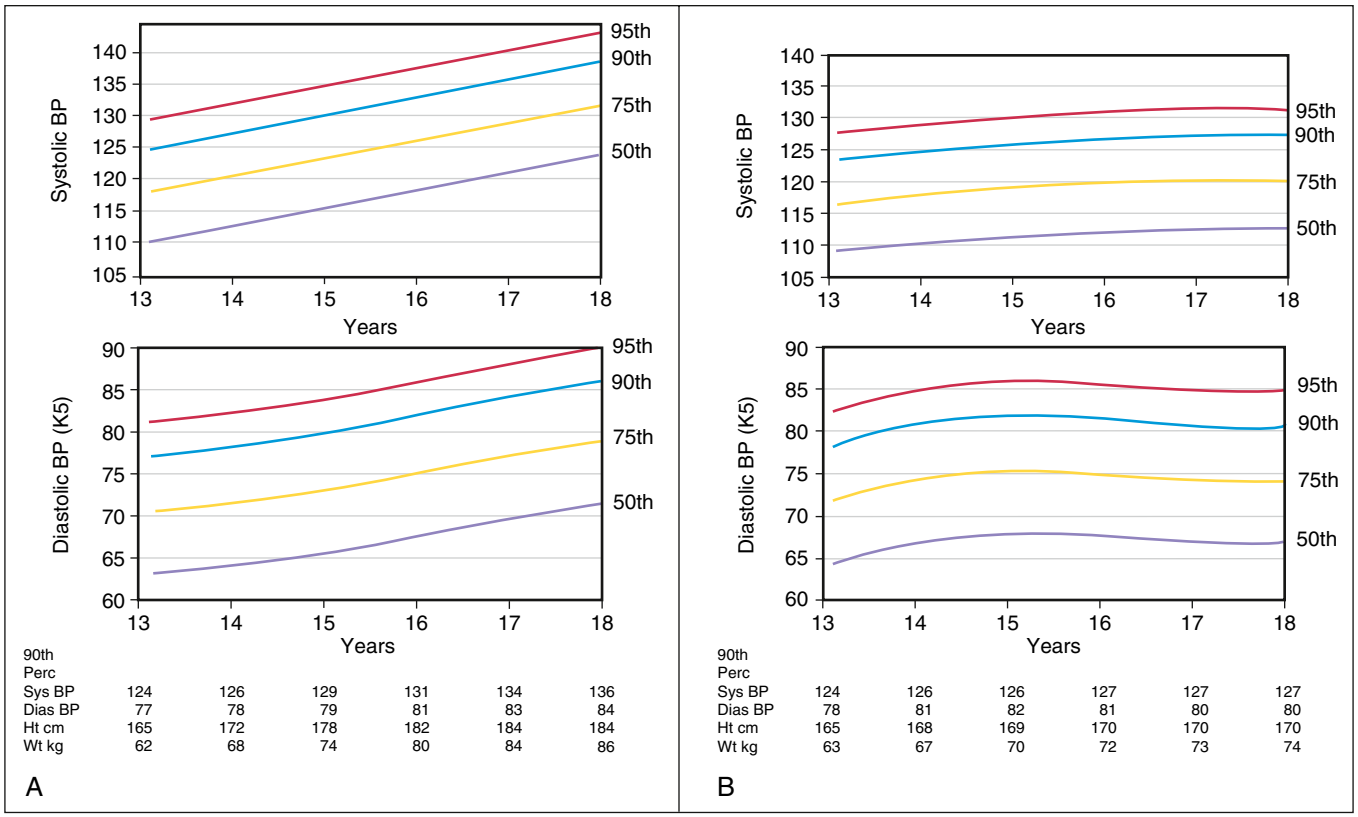

Fig. 471.3 Age-specific percentiles of blood pressure (BP) measurements: age 13-18 yr. **A**, Males 13-18 yr of age. **B**, Females 13-18 yr of age. Korotkoff phase V (K5) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD. Pediatrics. 1987;79:1–25. Copyright 1987 by the American Academy of Pediatrics.)*

Several types of **diastolic murmurs** (graded I-IV) can be identified. A **decrescendo diastolic murmur** is a blowing murmur usually along the left sternal border that begins with S_2 and diminishes toward mid-diastole. When louder and high-pitched, this murmur is usually associated with aortic valve insufficiency or pulmonary insufficiency related to pulmonary hypertension. When softer and low-pitched, this murmur is usually associated with pulmonary valve insufficiency in the absence of pulmonary hypertension. A to-and-fro murmur is typically noted after surgical repair of the pulmonary outflow tract in patients with tetralogy of Fallot. A **rumbling mid-diastolic murmur** at the left mid and lower sternal border may be caused by increased blood flow across the tricuspid valve, such as occurs with ASD or, much less often, because of actual stenosis of this valve. When this murmur is heard at the apex, it is caused by increased flow across the mitral valve, such as occurs with large left-to-right shunts at the ventricular level (VSDs), at the great vessel level (PDA, aortopulmonary shunts), or with increased flow because of mitral insufficiency. When an apical diastolic rumbling murmur is longer and is accentuated at the end of diastole (presystolic), it usually indicates anatomic mitral valve stenosis.

The absence of a precordial murmur does not rule out significant congenital or acquired heart disease. Congenital heart defects, some of which are ductal dependent, may not demonstrate a murmur if the ductus arteriosus closes. These lesions include pulmonary or tricuspid valve atresia and transposition of the great arteries. Murmurs may seem insignificant in patients with ASDs, anomalous pulmonary venous return, some forms of atrioventricular septal defects, coarctation of the aorta, or anomalous origin of a coronary artery. Careful attention to other components of the physical examination (growth failure, cyanosis, peripheral pulses, precordial impulse, heart sounds) increases the index of suspicion of congenital heart defects in these patients. In contrast, loud murmurs may be present in the absence of structural heart disease, for example, in patients with a large noncardiac arteriovenous malformation, mitral regurgitation caused by left ventricular dilation associated with myocarditis or cardiomyopathy, and severe anemia.

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as *functional, normal, insignificant,* or *innocent*. During routine random auscultation, >30% of children may have an innocent murmur at some time in their lives; this percentage increases when auscultation is done under nonbasal circumstances (high cardiac output because of fever, infection, or anxiety). The most common **innocent murmur** is a medium-loud, medium-pitched, vibratory or "musical," relatively short *systolic ejection murmur,* which is heard best along the left sternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 years of age. The intensity of the murmur often changes with respiration and position and may be attenuated or even disappear in the sitting or prone position. Innocent *pulmonic* murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. These are higher pitched, brief, early systolic murmurs of grades I-II in intensity and are best heard in the second left parasternal space with the patient in the supine position. Features suggestive of heart disease include murmurs that are holosystolic, grade III or higher, harsh, located at the left upper sternal border, and associated with an early or midsystolic click or an abnormal S_2.

A **venous hum** is another example of a common innocent murmur heard during childhood. Venous hums are produced by turbulence of blood in the jugular venous system; they have no pathologic significance and may be heard in the neck or anterior portion of the upper part of the chest. Appreciated as a soft humming sound heard in both systole and diastole, it can be exaggerated or made to disappear by

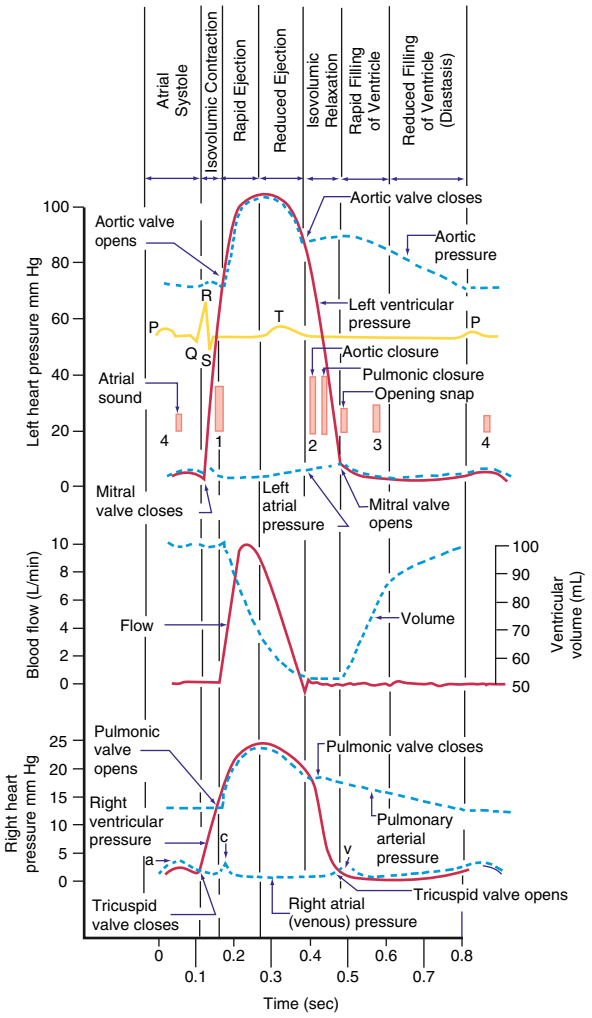

Fig. 471.4 Idealized diagram of the temporal events of a cardiac cycle (the Wiggers diagram).

varying the position of the head, or it can be decreased by lightly compressing the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease, particularly a PDA.

The lack of significance of an innocent murmur should be discussed with the child's parents. It is important to offer complete reassurance because lingering doubts about the importance of a cardiac murmur may have profound effects on child-rearing practices, most often in the form of overprotectiveness. An underlying fear that a cardiac abnormality is present may negatively affect a child's self-image and development. The physician should explain that an innocent murmur is simply a "noise" and does not indicate the presence of a cardiac defect. When asked, "Will it go away?" the best response is to state that because the murmur has no clinical significance, it does not matter whether it "goes away." Parents should be warned that the intensity of the murmur might increase during febrile illnesses, a time when, typically, another physician may examine the child (e.g., in the emergency department). With growth, however, innocent murmurs are less well heard and often disappear completely. If there is a suspicion of structural heart disease, additional studies are indicated to rule out a congenital heart defect. However, "routine" electrocardiographic, chest radiographic, and echocardiographic examinations should be avoided in well children with a clearly innocent murmur.

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Chapter 472

Laboratory Cardiac Evaluation

Daniel Bernstein

472.1 Radiologic Cardiac Assessment

Daniel Bernstein

Despite the widespread easy access to advanced imaging techniques, such as echocardiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), the chest x-ray film remains a highly valuable diagnostic tool and is often the first imaging study performed in a child suspected of having a cardiac defect. It can provide important information about cardiac size and shape, pulmonary blood flow (vascularity), pulmonary edema, and associated lung and thoracic anomalies that may be associated with congenital syndromes (e.g., skeletal dysplasias, extra or deficient number of ribs, abnormal vertebrae, diaphragmatic hernia, previous cardiac surgery). Combined with a careful physical examination, the chest radiograph can help the clinician to establish a diagnosis of congenital heart disease (CHD), as opposed to pulmonary disease, and to narrow the differential diagnosis to specific categories of CHD (e.g., left-to-right shunt lesions vs obstructive lesions).

The most frequently used measurement of cardiac size is the maximal width of the cardiac shadow in a posteroanterior (PA) chest film taken mid-inspiration. A vertical line is drawn down the middle of the sternal shadow, and perpendicular lines are drawn from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the **maximal cardiac width**. The **maximal chest width** is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the maximal cardiac width is more than half the maximal chest width (cardiothoracic ratio >50%), the heart is usually enlarged. Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position, which can be difficult to achieve in younger patients. A diagnosis of "cardiac enlargement" on expiratory or prone films is a common cause of unnecessary referrals and laboratory studies.

The **cardiothoracic ratio** is a less useful index of cardiac enlargement in infants than in older children because the horizontal position of the heart may increase the ratio to about 60% in the absence of true enlargement. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.

A *lateral* chest radiograph may be helpful in infants and in older children with pectus excavatum or other conditions that result in a narrow anteroposterior (AP) chest dimension. The heart may appear small in the lateral view and suggest that the apparent enlargement in the PA projection was caused by either the thymus (anterior mediastinum only) or flattening of the cardiac chambers as a result of a structural chest abnormality.

In the PA view, the left border of the cardiac shadow consists of three convex shadows produced, from above downward, by the aortic knob, the main and left pulmonary arteries, and the left ventricle (Fig. 472.1). In cases of moderate to marked left atrial enlargement, the atrium may be visualized between the pulmonary artery and the left ventricle. The right ventricular outflow tract (RVOT) does not contribute to the shadows formed by the left border of the heart. The aortic knob is not as easily seen in infants and children as in adults. The side of the aortic arch (left or right) can often be inferred as being opposite the side of the midline from which the air-filled trachea is visualized. This observation is important because a right-sided aortic arch is often present in

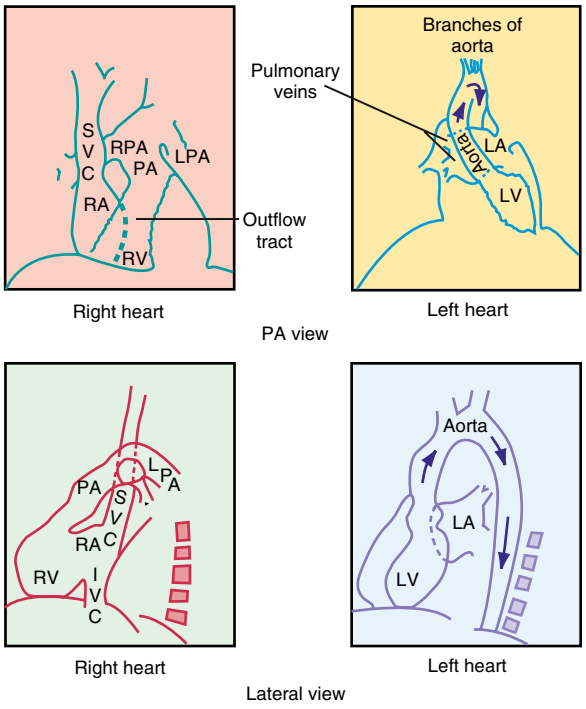

Fig. 472.1 Idealized diagrams showing normal position of the cardiac chambers and great blood vessels. IVC, Inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. *(Adapted and redrawn from Dotter CT, Steinberg I. Angiocardiographic interpretation. Radiology. 1949;153:513.)*

cyanotic CHD, particularly in tetralogy of Fallot. Three structures contribute to the right border of the cardiac silhouette. In the view from above, they are the superior vena cava, the ascending aorta, and the right atrium.

Enlargement of cardiac chambers (i.e., increased chamber volume) or major arteries and veins results in prominence of the areas in which these structures are normally outlined on the chest radiograph. In contrast, the electrocardiogram is a more sensitive and accurate index of **ventricular hypertrophy**, which is a thickening of the ventricular wall and may or may not be associated with dilation of the affected cardiac chamber.

The chest radiograph is also an important tool for assessing the degree of pulmonary vascularity. **Pulmonary overcirculation** is usually associated with left-to-right shunt lesions, whereas **pulmonary undercirculation** is associated with obstruction of the RVOT in cyanotic lesions. The esophagus is closely related to the great vessels, and a barium esophagogram can help delineate these structures in the initial evaluation of suspected vascular rings, although this has largely been supplanted by CT.

Echocardiographic examination best defines the morphologic features of intracardiac chambers, cardiac valves, and intracardiac shunts. CT is used as an adjunct to echocardiogram to evaluate extracardiac vascular morphology. MRI is used most often to provide a more quantitative assessment of inflammation as well as ventricular volumes, cardiac function, and shunt and regurgitant fractions than is possible with echocardiogram.

472.2 Electrocardiography

Daniel Bernstein

DEVELOPMENTAL CHANGES

The marked changes that occur in cardiac physiology and chamber dominance during the perinatal transition (see Chapter 470) are reflected in the evolution of the electrocardiogram (ECG) during the neonatal period. Because vascular resistance in the pulmonary and systemic circulations is nearly equal in a term fetus, the intrauterine work of the heart results in an equal mass of both the right and left ventricles. After birth, systemic vascular resistance (SVR) rises when the placental circulation is eliminated, and pulmonary vascular resistance (PVR) falls when the lungs expand. These changes are reflected in the ECG over the first few weeks of life as the right ventricular (RV) wall begins to thin.

The ECG demonstrates these anatomic and hemodynamic features principally by changes in QRS and T-wave morphologic features. Typically, pediatric ECGs include several additional leads rarely used in adults, such as V_3R and V_4R, which are mirror images of leads V_3 and V_4 and are important in the evaluation of **right ventricular hypertrophy** (RVH). On occasion, lead V_1 is inappropriately positioned too far leftward to reflect RV forces accurately. This problem is present particularly in premature infants, in whom the electrocardiographic electrode gel may produce contact among all the precordial leads. An additional lead used in children is V_7, located more laterally than V_6 and useful for assessing left-sided forces.

During the first postnatal days of life, right axis deviation, large R waves, and upright T waves in the right precordial leads (V_3R or V_4R and V_1) are the norm (Fig. 472.2). As PVR decreases in the first few days after birth, the right precordial T waves become negative. In the great majority of cases, this change occurs within the first 48 hours of postnatal life. Upright T waves that persist in leads V_3R, V_4R, or V_1 beyond 1 week of life are an abnormal finding indicating RVH or RV strain, even in the absence of QRS voltage criteria. The T wave in V_1 should never be positive before 6 years of age; however, it may remain negative into adolescence or early adulthood. This finding represents one of the most important yet subtle differences between pediatric and adult ECGs and is a common source of error when adult cardiologists interpret pediatric ECGs.

In a newborn the mean **QRS frontal-plane axis** normally lies in the range of +110 to +180 degrees, reflecting the codominance of the fetal right and left ventricles. The right-sided chest leads reveal a larger positive **(R)** than negative **(S)** wave and may do so for months because the right ventricle remains relatively thick throughout early infancy. Left-sided leads (V_5 and V_6) also reflect right-sided dominance in the early neonatal period, when the R:S ratio in these leads may be <1. A dominant R wave in V_5 and V_6, reflecting left ventricular (LV) forces, quickly becomes evident within the first few days of life (Fig. 472.3). As the child matures, the QRS axis gradually shifts leftward and the RV forces slowly regress. Leads V_1, V_3R, and V_4R display a prominent R wave until 6 months to 8 years of age. Most children have an R:S ratio >1 in lead V_4R until age 4 years. The T waves are inverted in leads V_4R, V_1, V_2, and V_3 during infancy and may remain so into the middle of the second decade of life and beyond. The processes of RV thinning and LV growth are best reflected in the QRS-T pattern over the right precordial leads. The diagnosis of RVH or left ventricular hypertrophy (LVH) in a pediatric patient can be made only with an understanding of the normal developmental physiology of these chambers at various ages until adulthood is reached. As the left ventricle becomes dominant, the ECG evolves to the characteristic pattern of older children (Fig. 472.4) and adults (Fig. 472.5).

Ventricular hypertrophy usually results in increased voltage in the R and S waves in the chest leads. The height of these deflections is governed by the proximity of the specific electrode to the surface of the heart; by the sequence of electrical activation through the ventricles, which can result in variable degrees of cancellation of right vs left forces; and by hypertrophy of the myocardium.

The diagnosis of **pathologic RVH** is difficult in the first week of postnatal life because physiologic RVH is a normal finding. Serial tracings are often necessary to determine whether marked right axis deviation and potentially abnormal right precordial forces or T waves, or both, will persist beyond the neonatal period (Fig. 472.6). In contrast, an adult ECG pattern (see Fig. 472.5) seen in a neonate suggests LVH. The exception is a premature infant, who may display a more "mature" ECG than a full-term infant (Fig. 472.7) as a result of lower PVR secondary

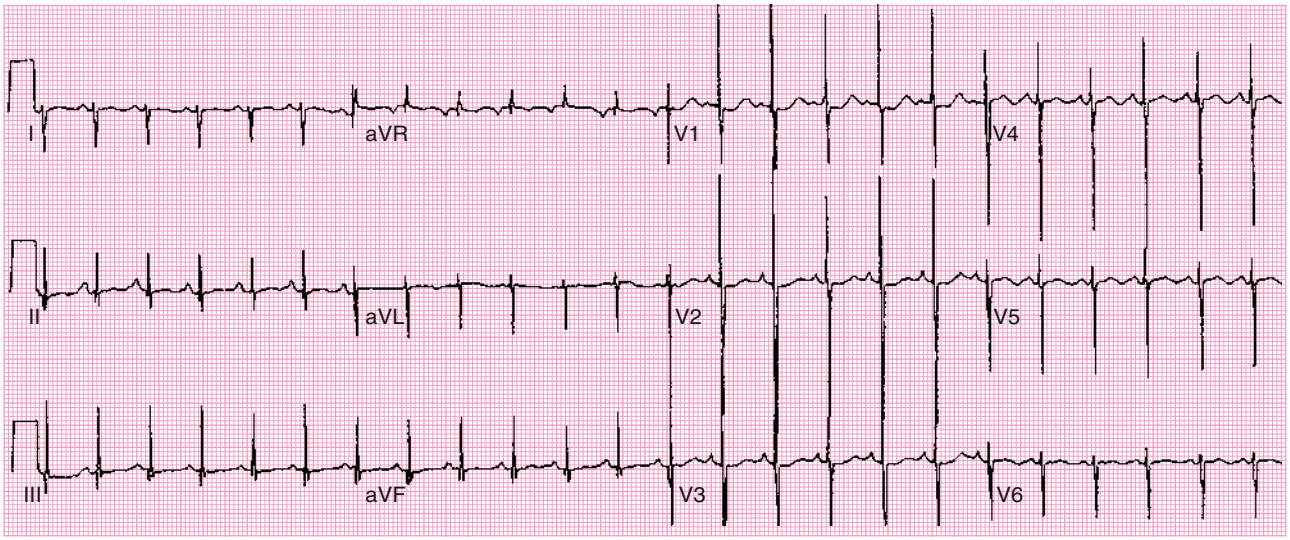

Fig. 472.2 Normal ECG from a 5-day-old, term-gestation infant. The frontal plane QRS axis is 150 degrees. There is prominent voltage in the precordial leads and a suggestion of right ventricular preponderance but not right ventricular hypertrophy. The QRS duration is 60 ms. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.2, p. 651).*

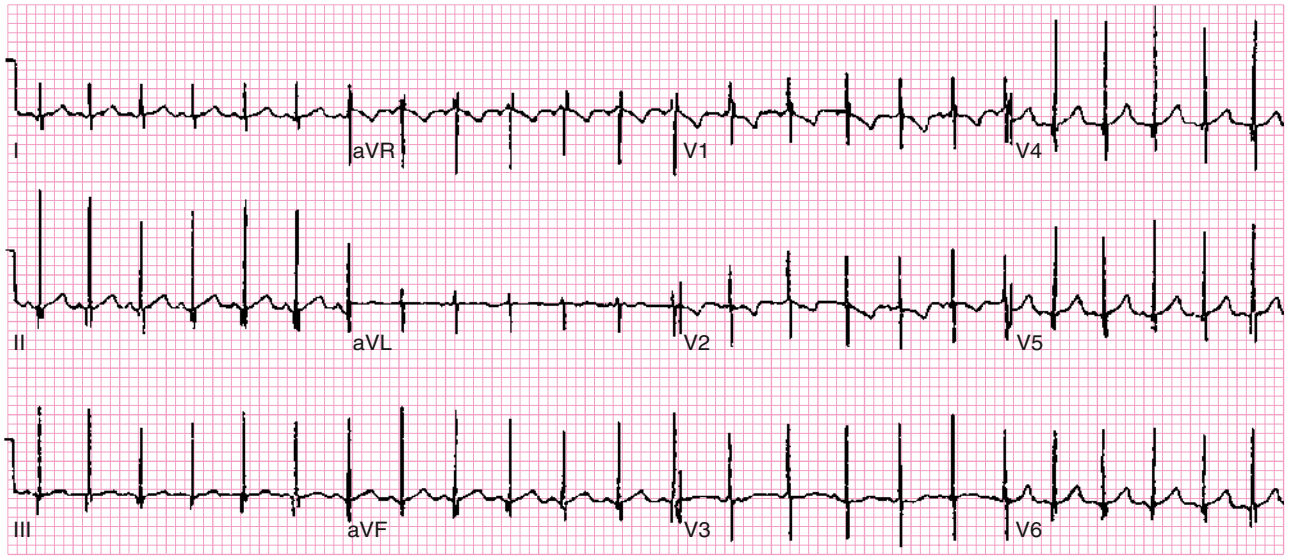

Fig. 472.3 Normal ECG from a healthy 8-mo-old infant. The frontal plane QRS axis is 60 degrees. There is less evidence of right ventricular preponderance than in the newborn tracing, with a smaller R wave in lead V_1 and smaller S wave in lead V_6. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.3, p. 652).*

to underdevelopment of the medial muscular layer of the pulmonary arterioles. Some premature infants display a pattern of generalized low voltage across the precordium.

The ECG should always be evaluated systematically to avoid overlooking a minor but important abnormality. One approach is to begin with an assessment of rate and rhythm, followed by a calculation of the mean frontal-plane QRS axis, measurements of segment intervals, assessment of voltages, and lastly assessment of ST and T-wave abnormalities.

RATE AND RHYTHM

A brief rhythm strip should be examined to assess whether a P wave always precedes each QRS complex. Using the full 12-lead ECG, the P-wave axis should then be estimated as an indication of whether the rhythm is originating from the **sinus node**. If the atria are situated normally in the chest, the P-wave axis should be oriented downward and to the left (i.e., should be upright in leads I and aVF and inverted in lead aVR). With atrial inversion **(situs inversus)**, the P wave may be inverted in lead I. Inverted P waves in leads II and aVF are seen in low atrial, nodal, or junctional rhythms. The absence of P waves indicates a rhythm originating more distally in the conduction system. In this case, the morphologic features of the QRS complexes are important in differentiating a **junctional** (usually a narrow QRS complex) from a **ventricular** (usually a wide QRS complex) rhythm.

P WAVES

Tall (>2.5 mm), narrow, and spiked P waves are indicative of **right atrial enlargement** and are seen in pulmonary stenosis, Ebstein anomaly of the tricuspid valve, tricuspid atresia, and sometimes cor pulmonale. These abnormal waves are most obvious in leads II, V_3R,

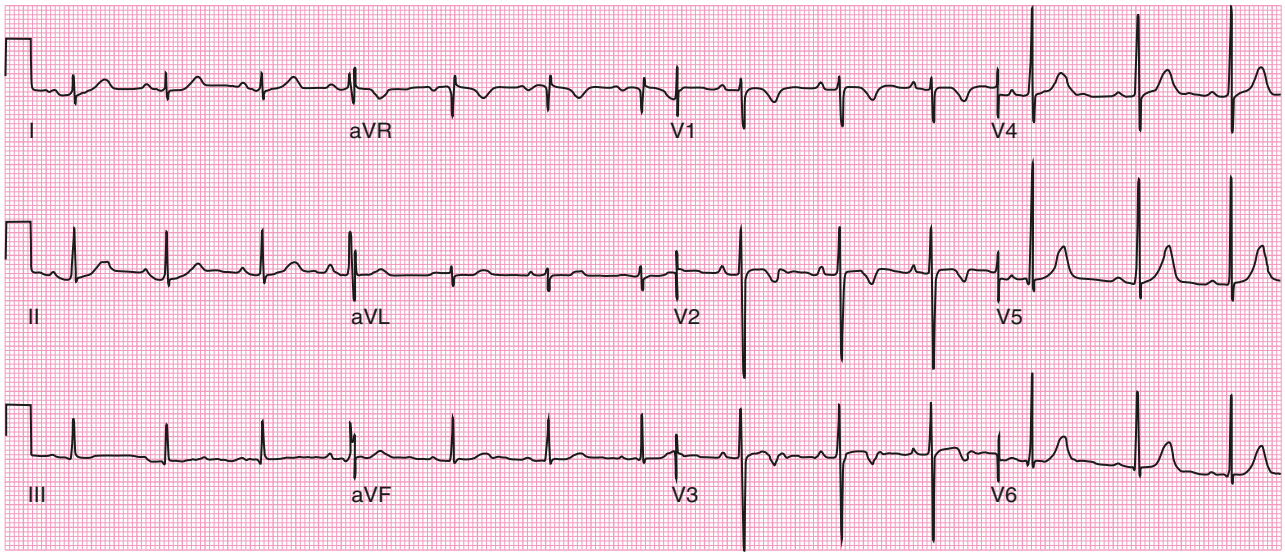

Fig. 472.4 Normal ECG from a healthy 3-yr-old child. The frontal plane QRS axis is 60 degrees. The R/S ratio in lead V_1 is less than 1, and there is no appreciable S wave in lead V_6. The R wave in lead V_6 is more prominent than that of the infant, suggesting more left ventricular preponderance but not left ventricular hypertrophy. *(From Gering LE, Knilans TK, Surawicz B, et al. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.4, p. 652).*

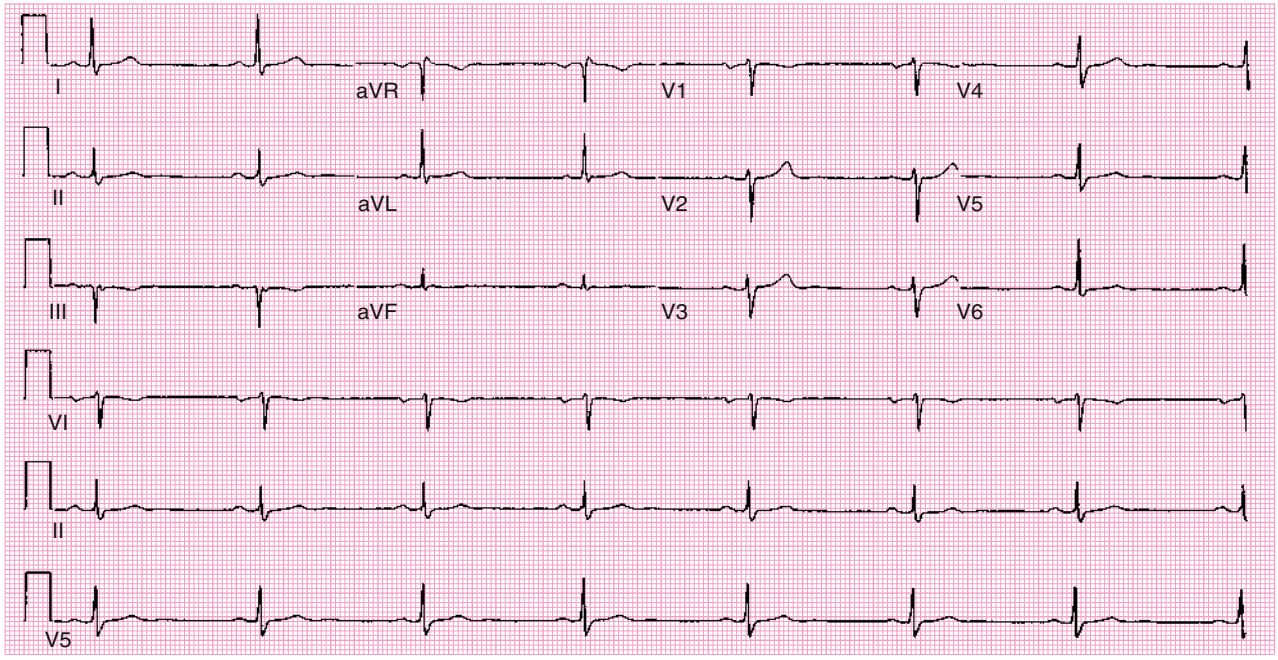

Fig. 472.5 Electrocardiogram of a normal 17-yr-old, a member of the school's track team. At this age the ECG should be similar to that in a normal adult: the dominant wave in V_1 should be the S wave and there is a normal R-wave progression, growing taller across the precordium from right to left. The heart rate is slow at 43 bpm (sinus bradycardia), which can be typical of a performance athlete. Note that all precordial lead T waves are positive, except for V_1. This R-wave progression pattern in a young infant, where there should be right ventricular dominance, would indicate the presence of left ventricular hypertrophy.

and V_1 (Fig. 472.8A). Similar waves are sometimes seen in thyrotoxicosis. **Broad P waves**, commonly **bifid** and sometimes **biphasic**, are indicative of **left atrial enlargement** (Fig. 472.8B). They are seen in some patients with large left-to-right shunts (ventricular septal defect [VSD], patent ductus arteriosus) and with severe mitral stenosis or mitral regurgitation. Left atrial enlargement, however, is one of the most common false-positive readings generated by computerized ECG machines. Flat P waves may be encountered in patients with hyperkalemia.

QRS COMPLEX

Right Ventricular Hypertrophy

For the most accurate assessment of ventricular hypertrophy, pediatric ECGs should include the right precordial leads V_3R and V_4R. The diagnosis of RVH depends on demonstration of the following changes (see Fig. 472.6): (1) a qR pattern in the RV surface leads; (2) a positive T wave in leads V_3R-V_4R and V_1-V_3 between ages 6 days and 6 years; (3) a monophasic R wave in V_3R, V_4R, or V_1; (4) an rsR′ pattern in the right precordial leads with the second R wave

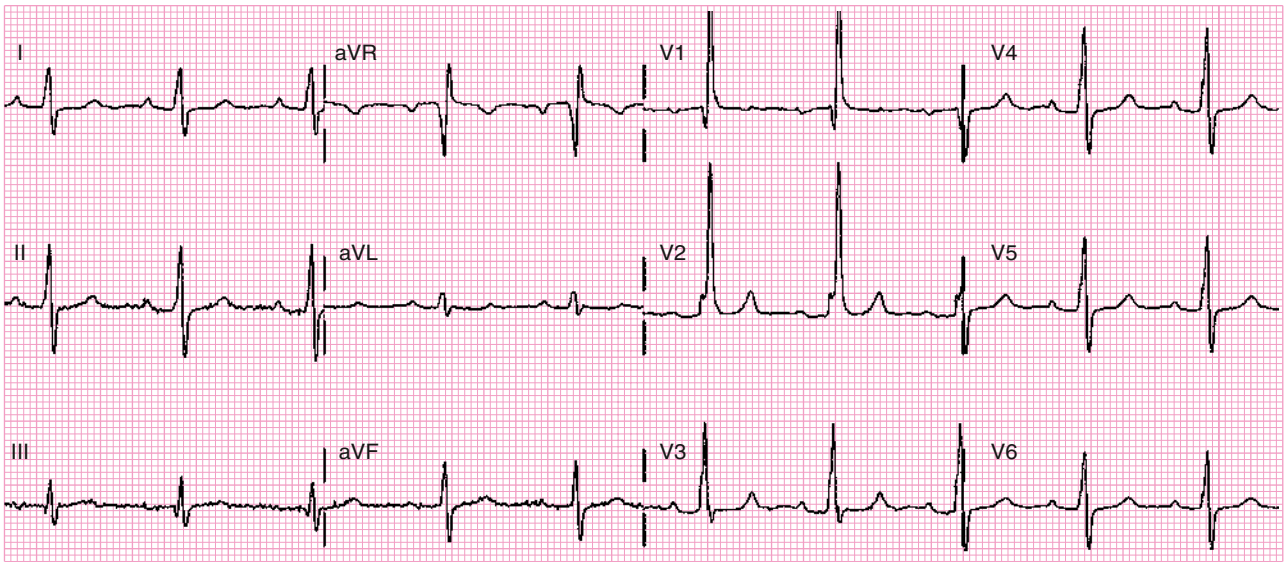

Fig. 472.6 Electrocardiogram of an infant with right ventricular hypertrophy (tetralogy of Fallot). Note the tall R waves in the right precordial leads (V_1-V_2) and deep S waves in V_6. The R-wave progression (taller in the right precordial leads vs the left) is counter to the normal pattern.

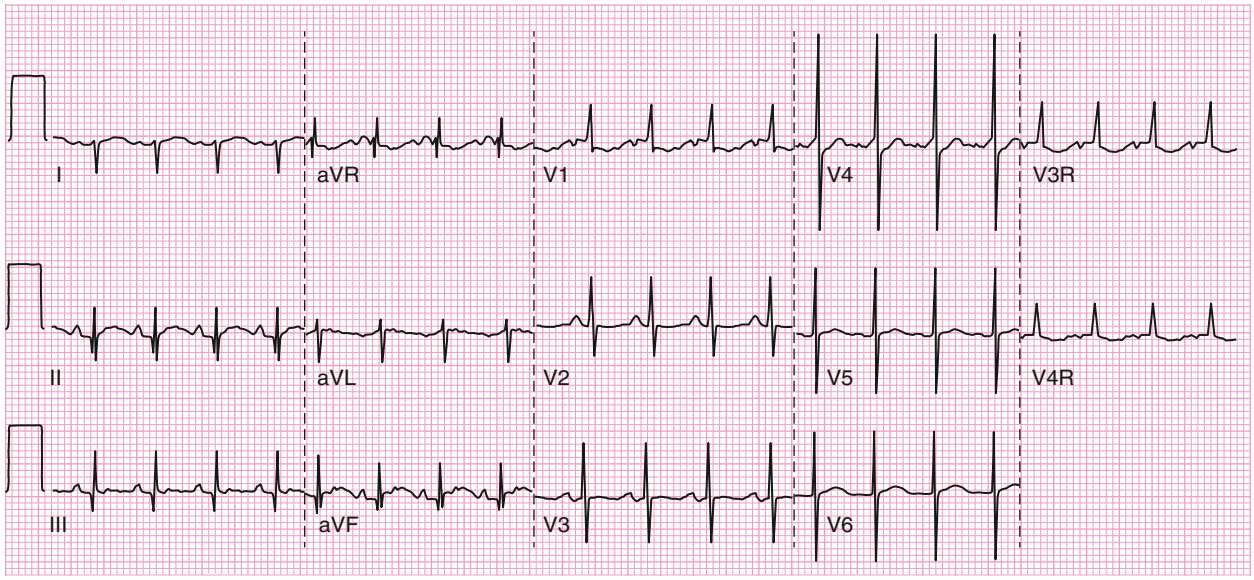

Fig. 472.7 Normal ECG from an 8-day-old, 28-wk-gestation premature infant. The frontal plane QRS axis is 150 degrees, there is a monophasic R wave in lead V_1, and the R/S ratio is less than 1 in lead V_6. This illustrates relative right ventricular preponderance without right ventricular hypertrophy. The QRS duration is less than 40 ms. *(From Gering LE, Knilans TK, Surawicz B, Tavel ME. Normal electrocardiograms in the fetus, infants, and children. In: Surawicz B, Knilans TK. Chou's Electrocardiography in Clinical Practice, 6th ed. Philadelphia: Saunders; 2008: Fig. 28.1, p. 650).*

taller than the first; (5) age-corrected increased voltage of the R wave in leads V_3R-V_4R or the S wave in leads V_6-V_7, or both; (6) marked right axis deviation (>120 degrees in patients beyond the newborn period); and (7) complete reversal of the normal adult precordial RS pattern. At least two of these changes should be present to support a diagnosis of RVH.

Abnormal ventricular loading can be characterized as either pressure overload (as a result of RVOT obstruction, as in pulmonic stenosis) or volume overload (as a result of a left-to-right shunt as in atrial septal defect [ASD], semilunar valve regurgitation, or dilated cardiomyopathy). These two types of abnormal loads result in distinct electrocardiographic patterns. The **pressure overload pattern** is characterized by tall, pure R waves in the right precordial leads. In older children, the T waves in these leads are initially upright and later become inverted. In infants and children <6 years, the T waves in V_3R-V_4R and V_1 are abnormally upright. The **volume overload pattern** (typically seen in patients with ASD) is characterized by an rsR′ pattern (Fig. 472.9) and a slightly increased QRS duration (which is known as a *minor right ventricular conduction delay* rather than a true bundle branch block). Patients with mild to moderate pulmonary stenosis may also exhibit an rsR′ pattern in the right precordial leads.

Left Ventricular Hypertrophy

The following features indicate the presence of LVH (Fig. 472.10): (1) increased voltage (for age) of the S wave in V_3R and V_1 or the R wave in V_6-V_7, or both. In older children and adults, the criteria for LVH **(Sokolow index)** is a combination of S wave in V_1 or V_2 plus R wave in V_5 or V_6 ≥35 mm and (2) a deep Q wave in the left precordial leads. Remember that an infant with an ECG that would be considered "normal" for an older child may in fact have LVH; therefore reference to

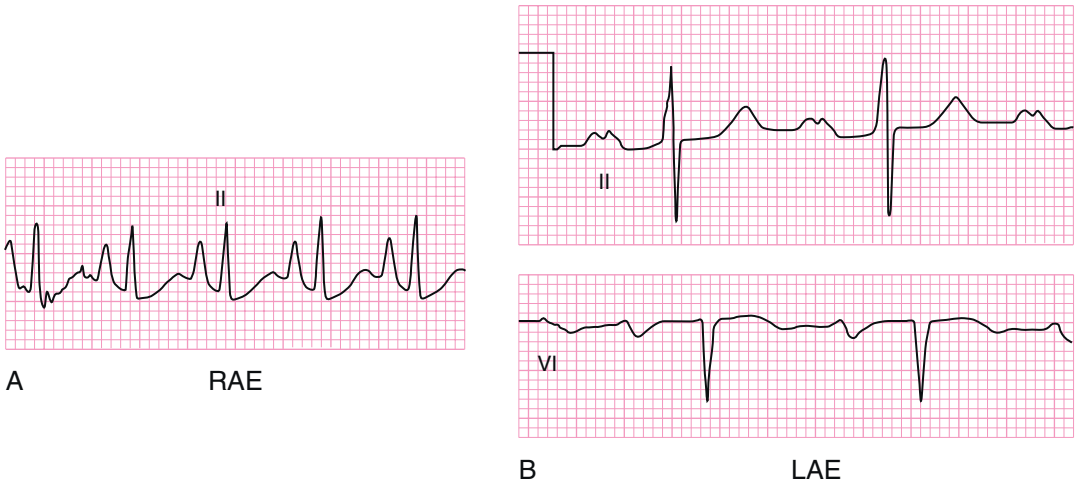

Fig. 472.8 Atrial enlargement. **A,** Peaked narrow P waves in lead II characteristic of right atrial enlargement (RAE). **B,** Wide, bifid, M-shaped P waves in lead II and biphasic p waves in lead V_1 typical of left atrial enlargement (LAE).

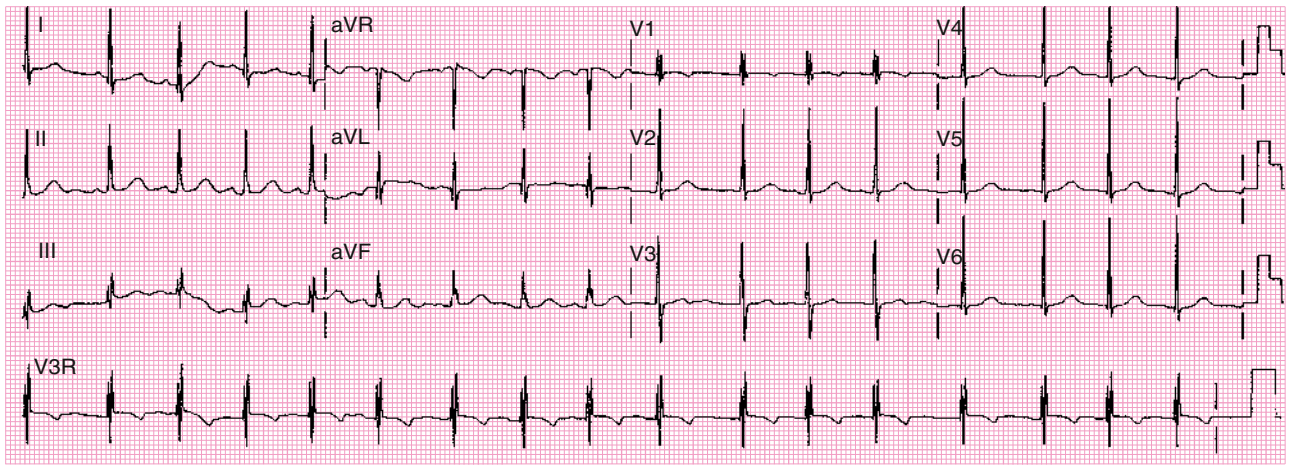

Fig. 472.9 Electrocardiogram showing a minor right ventricular conduction delay characterized by an RsR′ pattern in V_1. Note that the QRS duration is not prolonged (60 msec) as it would be if this were a right bundle branch block (RBBB).

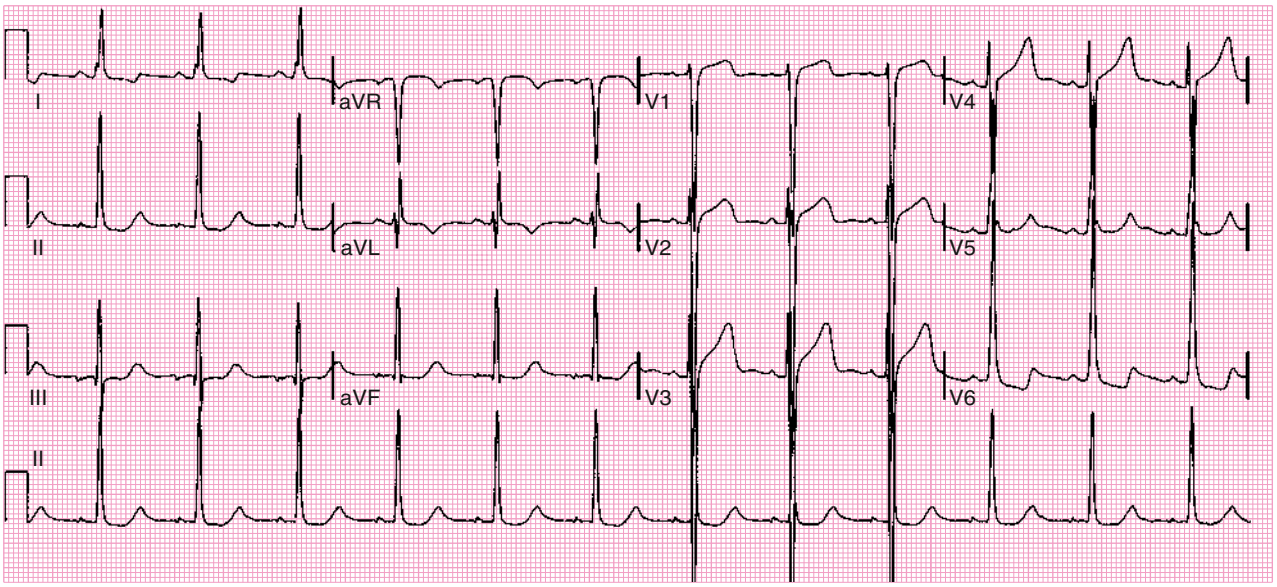

Fig. 472.10 Electrocardiogram showing left ventricular hypertrophy (LVH) in a 12-yr-old child with aortic stenosis. Note the deep S waves in V_1-V_3 and tall R in V_5-V_6. In addition, T-wave inversion is present in lead V_6, a sign of left ventricular strain.

standard voltages for age is always important. Further evidence for LVH includes depression of the ST segments and inversion of the T waves in the left precordial leads (V_5, V_6, and V_7), known as a **left ventricular strain** pattern—these findings suggest the presence of more severe hypertrophy.

Bundle Branch Block

A complete **right bundle branch block** (RBBB; prolonged QRS complex, which is usually upright with an rSR′ in lead V_1; wide S wave in lead V_6) may be congenital or may be acquired after surgery for CHD, especially when a right ventriculotomy has been performed, as in repair of the tetralogy of Fallot. **Left bundle branch block** (LBBB; prolonged QRS complex, which is usually upright with an rSR′ in lead V_6; wide S wave in lead V_1) is less common in children; this pattern is often seen in adults with cardiomyopathy, but much less in children with cardiomyopathy. LBBB may be seen after surgery on the aortic or mitral valve caused by surgical injury to one of the left-sided conduction bundles. Alternatively, a bundle branch block pattern may be indicative of a bypass tract associated with one of the preexcitation syndromes (see Chapter 484).

P-R AND Q-T INTERVALS

The duration of the P-R interval shortens with increasing heart rate; assessment of this interval should be based on age- and rate-corrected nomograms. A long P-R interval is diagnostic of a **first-degree heart block**, the cause of which may be congenital, postoperative (after open heart surgery), inflammatory (myocarditis, pericarditis, Lyme disease, rheumatic fever), or pharmacologic (digitalis, calcium channel blockers).

The duration of the Q-T interval varies with the cardiac rate; a corrected Q-T interval (Q-Tc) can be calculated by dividing the measured Q-T interval by the square root of the preceding R-R interval. A normal Q-Tc should be <0.45. It is often lengthened with hypokalemia and hypocalcemia; in the former, a U wave may be noted at the end of the T wave (Fig. 472.11). A significant number of medications can also lengthen the Q-T interval, so a careful history of medication exposure is important in evaluating a patient with a borderline or long QT interval. A congenitally prolonged Q-T interval may also be seen in children with one of the long QT syndromes (Fig. 472.12). These patients are at high risk for ventricular arrhythmias, including a dangerous form of ventricular tachycardia known as **torsades de pointes**, and sudden death (see Chapter 484.5).

ST SEGMENT AND T-WAVE ABNORMALITIES

Coronary ischemia, leading to typical ST and T-wave abnormalities seen in adults, is rare in children. A slight elevation of the ST segment is often seen in normal teenagers, especially males, and is attributed to **early repolarization** of the heart (Fig. 472.13). It can sometimes be difficult to distinguish between ischemic ST segment changes and benign early repolarization; however, the following characteristics suggest early repolarization: (1) ST elevation limited to the lateral leads (V_5-V_6), (2) a characteristic notch at the J point (junction between the end of the QRS and the beginning of the ST segment), and (3) a concave rather than convex ST segment. Lack of any concerning symptoms is also critical. Early repolarization often resolves with exercise-induced tachycardia. In pericarditis, irritation of the epicardium may cause elevation of the ST segment, followed by abnormal T-wave inversion as healing progresses.

Depression of the ST segment may also occur in coronary ischemia or in any condition that produces myocardial injury, including severe anemia, carbon monoxide poisoning, glycogen storage disease of the heart, myocardial tumors, and mucopolysaccharidoses. An aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those of acute myocardial infarction in adults. ECG findings of ischemia may be seen in patients with Kawasaki disease who have developed coronary artery aneurysms (see Chapters 208 and 493.1). Similar changes may occur in patients with other rare abnormalities of the coronary arteries and in those with cardiomyopathy, even in the presence of normal coronary arteries. These patterns are often misread in young infants because of the unfamiliarity of pediatricians with this "infarct" pattern, and thus a high index of suspicion must be maintained in infants with dilated cardiomyopathy or with symptoms compatible with coronary ischemia (e.g., inconsolable crying).

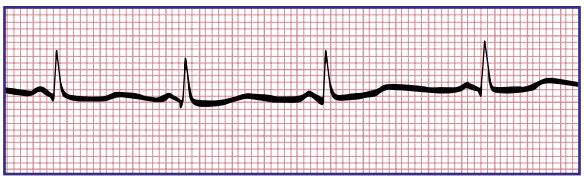

Fig. 472.12 Prolonged Q-T interval in a patient with long QT syndrome.

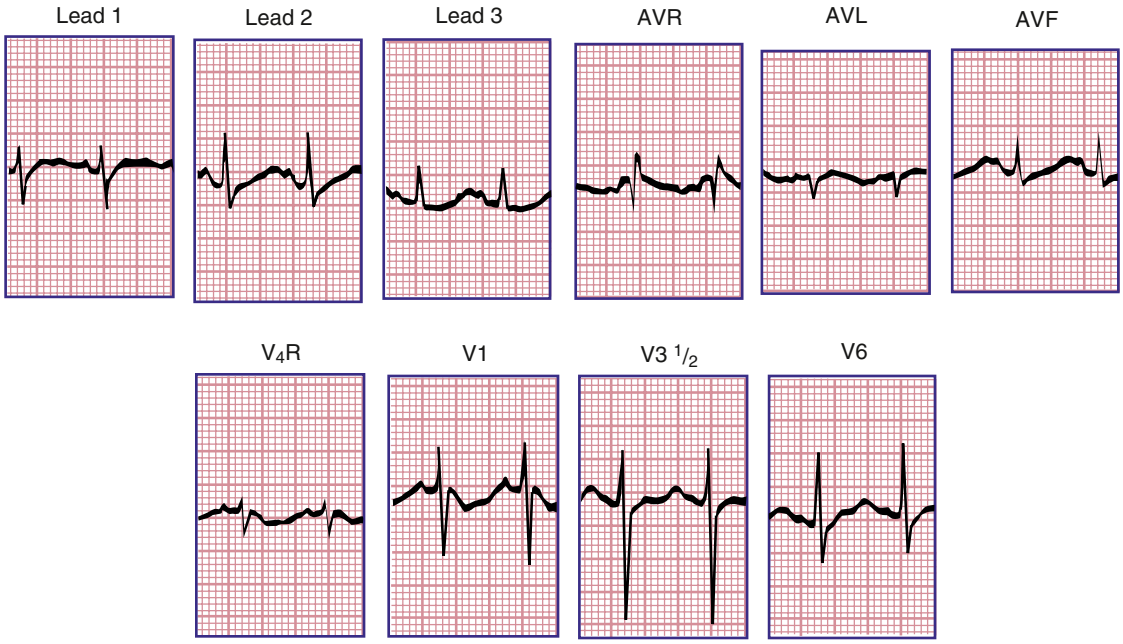

Fig. 472.11 Electrocardiogram in hypokalemia. Serum potassium, 2.7 mEq/L; serum calcium, 4.8 mEq/L at the time of the tracing. Note the widened TU wave and depression of the ST segment in V_4R, V_1, and V_6.

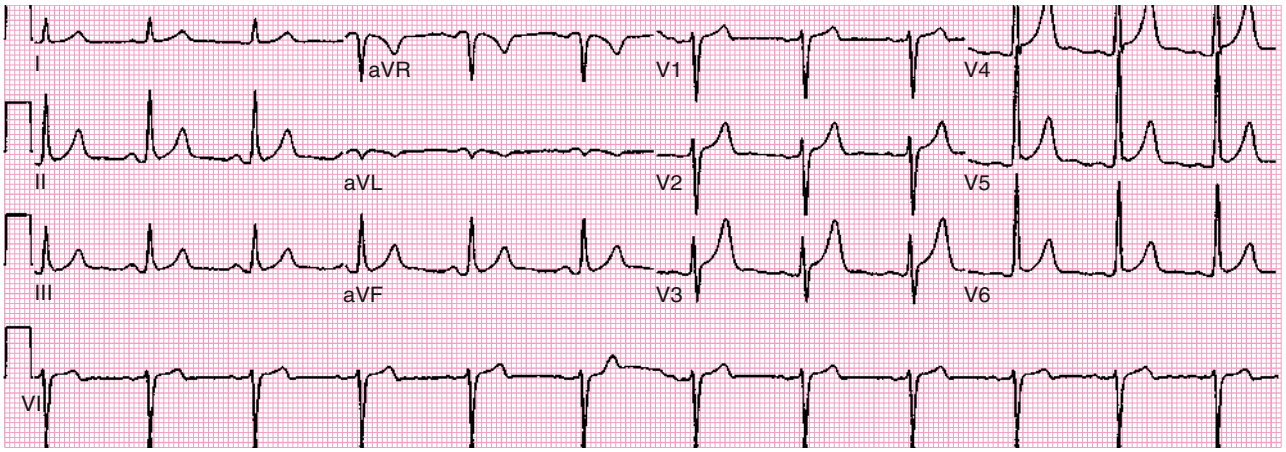

Fig. 472.13 Early repolarization seen in the mid-precordial to lateral leads (V_2-V_5) in a teenage boy. These minor ST segment elevations, with typical concave slope and combined with a high J point, suggest this is a benign variant and not true ischemia.

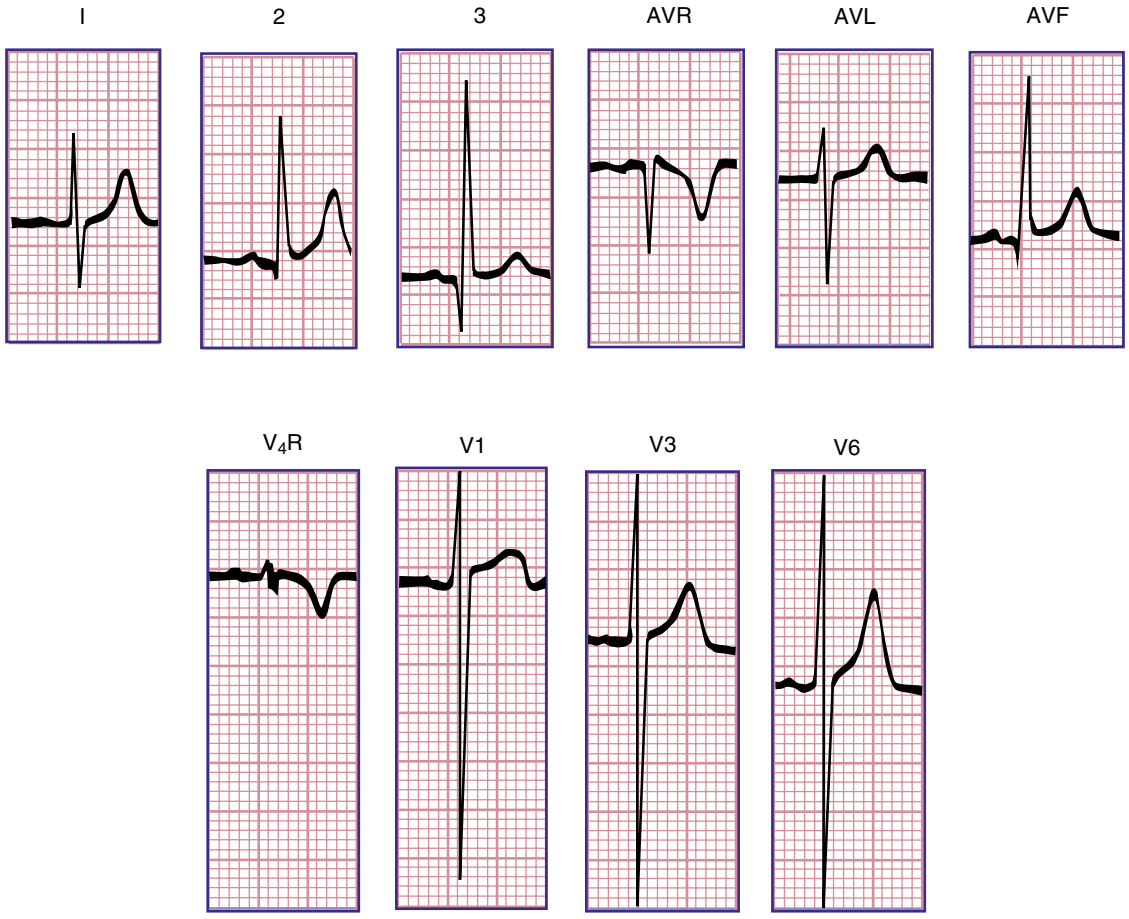

Fig. 472.14 Electrocardiogram in hyperkalemia. Serum potassium, 6.5 mEq/L. Note the tall, tent-shaped T waves, especially in leads 1, 2, and V_6.

T-wave inversion may occur in myocarditis and pericarditis, or it may be a sign of either RVH or LVH and ventricular strain. Hypothyroidism may produce flat or inverted T waves in association with generalized low voltage. In hyperkalemia, the T waves are usually of high voltage and are tent shaped (Fig. 472.14), although tall T waves can be an early sign of myocardial infarction.

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472.3 Hematologic Data in Cardiovascular Evaluation

Daniel Bernstein

In acyanotic infants with large left-to-right shunts, the onset of heart failure often coincides with the nadir of the normal physiologic anemia of infancy. Increasing the hematocrit in these patients to >40% may decrease shunt volume and result in an improvement in symptoms; however, this form of treatment is generally reserved for infants who are not otherwise surgical candidates (extremely premature infants or others in whom surgery is delayed for other reasons). In these select infants, regular evaluation of the hematocrit and booster transfusions when appropriate may be helpful in improving growth.

Polycythemia is frequently noted in chronically *cyanotic* patients with right-to-left shunts. Patients with severe polycythemia, rarely seen in this age of early surgical repair, are in a delicate balance between the risks of intravascular thrombosis and a bleeding diathesis. The preparation of cyanotic, polycythemic patients for elective noncardiac surgery, such as dental extraction, includes evaluation and treatment of abnormal coagulation.

Because of the high viscosity of polycythemic blood (hematocrit >65%), patients with unrepaired cyanotic CHD are at risk for the development of **vascular thromboses**, especially of cerebral veins. Dehydration increases the risk of thrombosis, and thus adequate fluid intake must be maintained during hot weather or intercurrent gastrointestinal illnesses. Diuretics should be used with caution in these patients and may need to be decreased if fluid intake is a concern. Polycythemic infants with concomitant **iron deficiency** are at even greater risk for cerebrovascular accidents, thought to be the result of the decreased deformability of microcytic red blood cells. Iron therapy may reduce this risk, but surgical repair of the cardiac anomaly is the best therapy.

Severely cyanotic patients who are inoperable should have periodic determinations of hemoglobin and hematocrit. Increasing polycythemia is often associated with headache, fatigue, dyspnea, or a combination of these conditions. Partial exchange transfusion may be required to treat symptomatic (most often headache or chest pain) individuals whose hematocrit has risen to the 65–70% level. This procedure is not without risk, especially in patients with an extreme elevation in pulmonary vascular resistance. Because these patients do not tolerate wide fluctuations in circulating blood volume, blood should be replaced with fresh-frozen plasma or albumin.

472.4 Echocardiography

Daniel Bernstein

Transthoracic echocardiography (TTE) has replaced cardiac catheterization for the *diagnosis* of most forms of CHD. The echocardiographic examination can be used to evaluate cardiac structures in congenital heart lesions using two-dimensional (2D) and three-dimensional (3D) imaging, estimate intracardiac pressures and gradients across stenotic valves and vessels using **echo-Doppler** and color flow Doppler, quantitate cardiac contractile function (both systolic and diastolic), determine the direction of flow across a defect, examine the integrity of the coronary arteries, and detect the presence of vegetations from endocarditis, pericardial fluid, cardiac tumors, and chamber thrombi.

Echocardiography may also be used to assist in the performance of interventional procedures, including pericardiocentesis, balloon atrial septostomy (see Chapter 480.2), ASD or VSD closure, transcatheter valve implantation, and endocardial biopsy. **Transesophageal echocardiography** (TEE) is used routinely to monitor ventricular function in patients during surgical procedures and can provide an immediate assessment of the results of surgical repair of congenital heart lesions. A complete TTE examination usually entails a combination of M-mode and 2D and 3D imaging, as well as pulsed, continuous, and color Doppler flow studies. Doppler tissue imaging provides a more quantitative assessment of ventricular systolic and diastolic function.

M-MODE ECHOCARDIOGRAPHY

M-mode echocardiography displays a one-dimensional slice of cardiac structure varying over time (Fig. 472.15). It is used mostly for the measurement of cardiac dimensions (wall thickness and chamber size) and cardiac function (fractional shortening, wall thickening). M-mode echocardiography is also useful for assessing the motion of intracardiac structures: the opening and closing of valves and movement of free walls and septa (Fig. 472.16). The most frequently used index of cardiac function in children is **percent fractional shortening** (%FS), which contrasts to adults, where **ejection fraction** is the most common functional measurement. %FS is calculated as (LVED − LVES)/LVED, where LVED is left ventricular dimension at end diastole and LVES is left ventricular dimension at end systole. Normal fractional shortening is approximately 28–42%. Other M-mode indices of cardiac function include the mean velocity of fiber shortening (mean V_{CF}), systolic time intervals (LVPEP = LV preejection period, LVET = LV ejection time), and isovolemic contraction time. M-mode assessments of cardiac function are more susceptible to errors because of differences in wall motion between different segments of the heart (more frequently seen in adults with ischemic heart disease, but which can be seen in

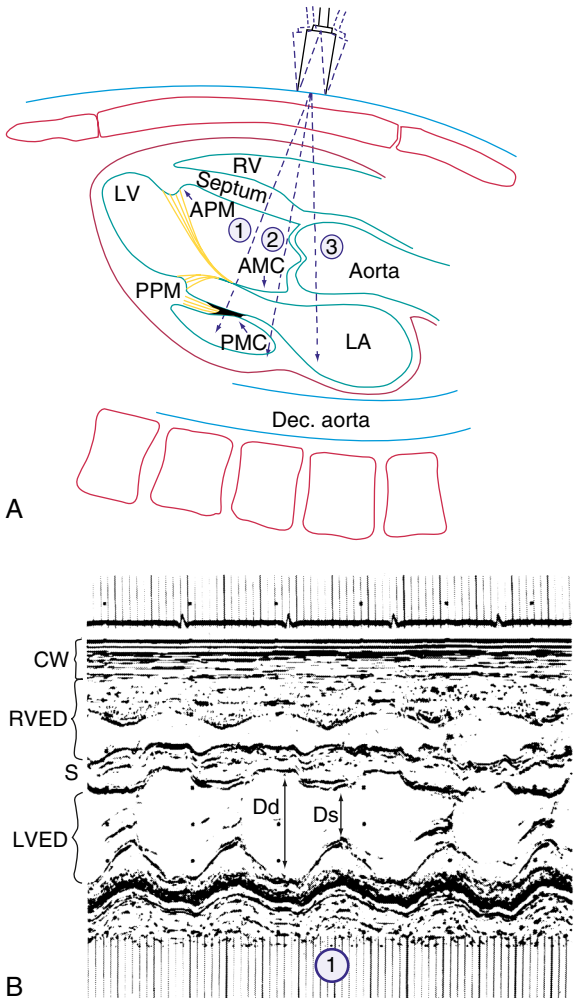

Fig. 472.15 M-mode echocardiogram. A, Diagram of a sagittal section of a heart showing the structures traversed by the echo beam as it is moved superiorly to positions (1), (2), and (3). B, Echocardiogram from transducer position (1); this view is the best one for measuring cardiac dimensions and fractional shortening. Fractional shortening is calculated as (LVED − LVES)/LVED. AMC, Anterior mitral cusp; APM, anterior papillary muscle; Dec. aorta, descending aorta; LA, left atrium; LV, left ventricle; PMC, posterior mitral cusp; PPM, posterior papillary muscle; RV, right ventricle. CW, Chest wall; Ds, LV dimension in systole; LVED, LV dimension at end diastole (Dd); RVED, RV dimension at end diastole.

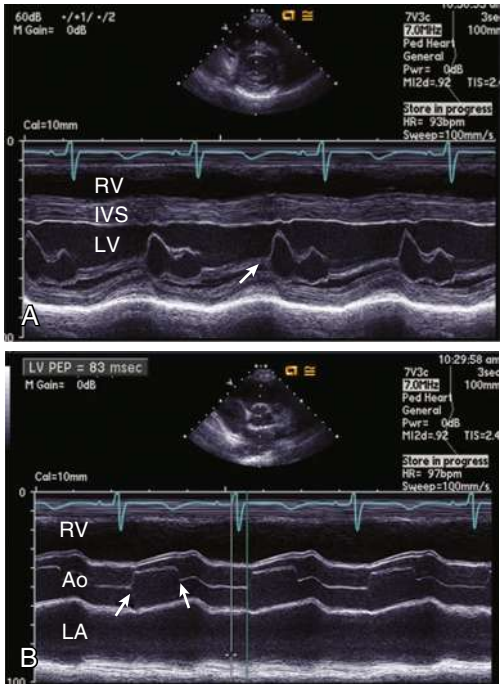

Fig. 472.16 M-mode echocardiograms. The small figure at the top of each panel shows the 2D parasternal short-axis echocardiogram image from which the M-modes are derived. The cursor can be seen midway through the image, indicating the one-dimensional line through which the M-mode is being sampled. **A,** M-mode echocardiogram of a normal mitral valve. *Arrow* shows the opening of the anterior leaflet in early diastole (see ECG tracing earlier for reference). **B,** M-mode echocardiogram of a normal aortic valve. The opening and closing of the aortic leaflets in systole are outlined by the two *arrows*. Ao, Aorta; IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

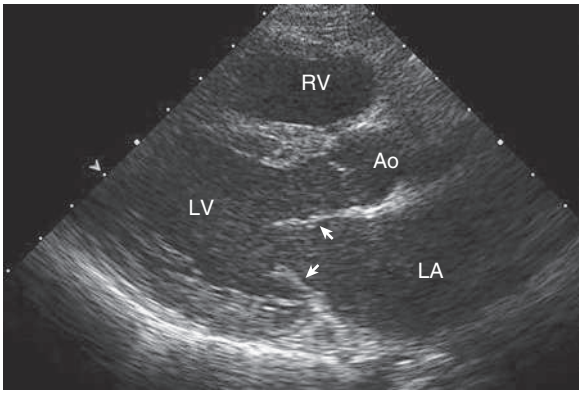

Fig. 472.17 Normal parasternal long-axis echocardiographic window. The transducer is angulated slightly posteriorly, imaging the left-sided cardiac structures. If the transducer were to be angulated more anteriorly, the right ventricular structures would be imaged. The mitral valve leaflets can be seen in the partially open position in early diastole *(arrows)*. The closed aortic valve leaflets can be seen just below the label Ao (aorta). LA, Left atrium; LV, left ventricle; RV, right ventricle.

children with congenital and acquired heart disease, especially after surgical repair).

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography provides a real-time image of cardiac structures. The contracting heart is imaged using several standard views, including parasternal long axis (Fig. 472.17), parasternal short axis (Fig. 472.18), apical four-chamber (Fig. 472.19), subcostal (Fig. 472.20), and suprasternal (Fig. 472.21), each of which emphasizes specific structures. Two-dimensional echocardiography

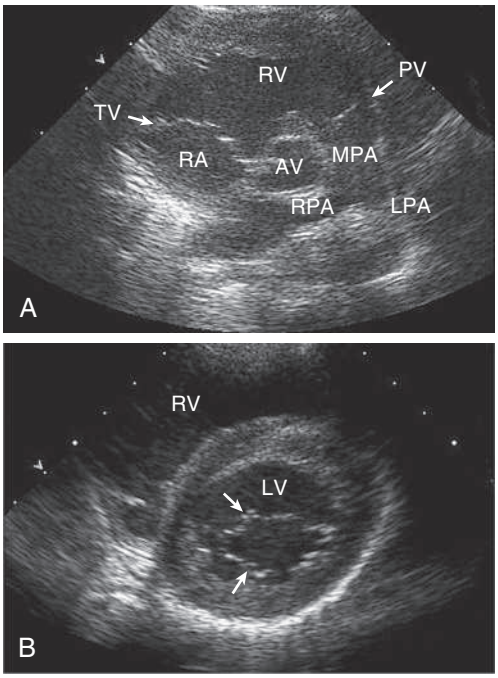

Fig. 472.18 Normal parasternal short-axis echocardiographic windows. **A,** With the transducer angled superiorly and rightward, the aortic valve (AV) is imaged, surrounded by both inflow and outflow portions of the right ventricle (RV). **B,** With the transducer angled inferiorly and leftward, the left ventricular chamber is imaged along with a cross-sectional view of the mitral valve *(arrows)*. LPA, Left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; TV, tricuspid valve. LV, left ventricle; RV, right ventricle.

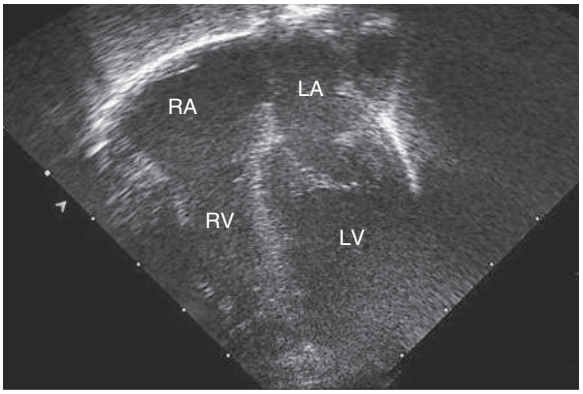

Fig. 472.19 Normal apical four-chamber echocardiographic window showing all four cardiac chambers and both atrioventricular valves opened in diastole. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

has replaced cardiac angiography for the preoperative diagnosis and follow-up of the vast majority of congenital heart lesions. However, when information from the cardiac examination or other studies is not consistent with the echocardiogram, or in very complex defects, cardiac catheterization remains an important tool to confirm the anatomic diagnosis and evaluate the degree of physiologic derangement. MRI is an extremely valuable adjunct to provide a better quantification of ventricular size and function. Cardiac CT is another modality that is valuable to assess cardiac and adjacent vascular structures.

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography displays blood flow based on the change in frequency imparted to sound waves by the movement of

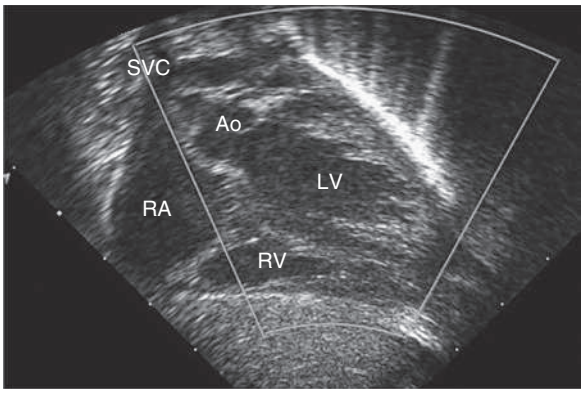

Fig. 472.20 Normal subcostal echocardiographic window showing the left ventricular outflow tract. The right-sided structures are not fully imaged in this view. Ao, Ascending aorta; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

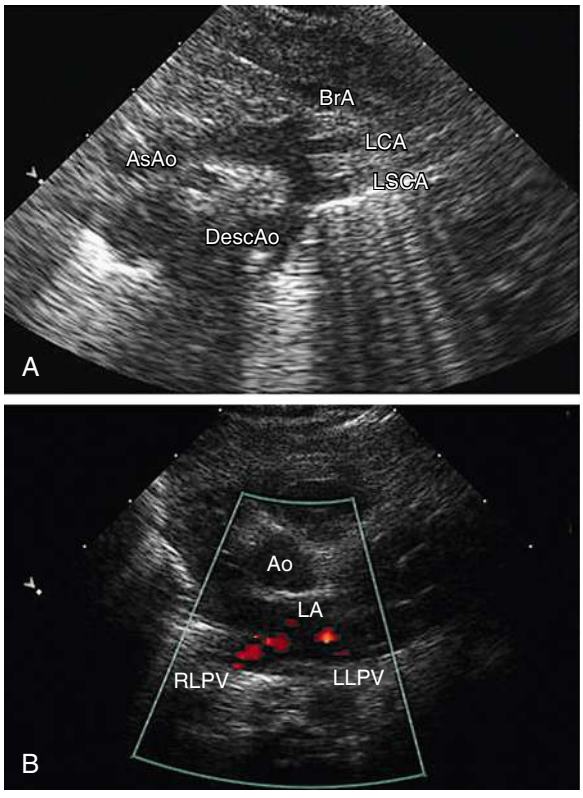

Fig. 472.21 **A,** Normal suprasternal echocardiographic window showing the aortic arch and its major branches. **B,** Normal high parasternal window showing color Doppler imaging of normal pulmonary venous return to the left atrium (LA) of both right (RLPV) and left (LLPV) lower pulmonary veins. AsAo, Ascending aorta; BrA, brachiocephalic artery; DescAo, descending aorta; LCA, left carotid artery; LSCA, left subclavian artery.

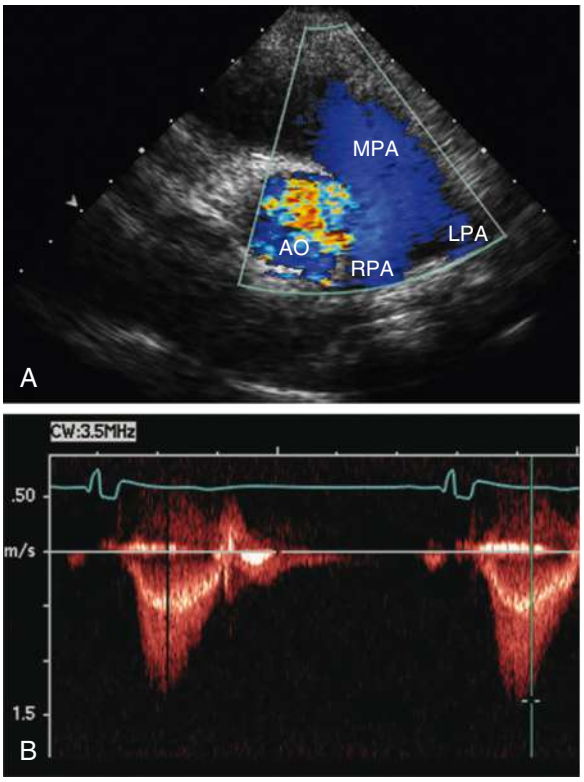

Fig. 472.22 Color and pulsed Doppler evaluation of pulmonary arterial flow. **A,** Color Doppler evaluation of a parasternal short-axis view showing normal flow through the pulmonary valve to the main and branch pulmonary arteries. The color of the Doppler flow is *blue,* indicating that the flow is moving away from the transducer (which is located at the top of the figure, at the apex of the *triangular* ultrasound window). Note that the color assigned to the Doppler signal does not indicate the oxygen saturation of the blood. **B,** Pulsed-wave Doppler flow pattern through the pulmonary valve showing a low velocity of flow (<1.5 m/sec), indicating the absence of a pressure gradient across the valve. The envelope of the flow signal is below the line, indicating that the flow is moving away from the transducer. AO, Aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

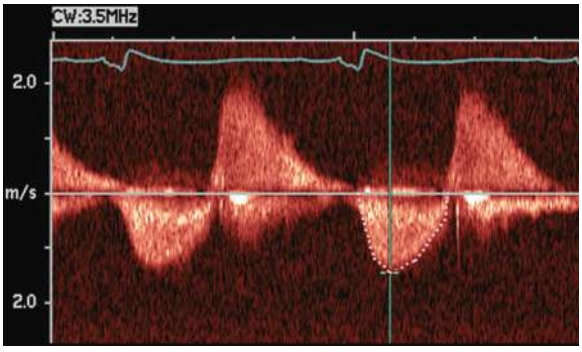

Fig. 472.23 Doppler evaluation of a patient who had previously undergone repair of tetralogy of Fallot and who has mild pulmonary stenosis and moderate pulmonary regurgitation. The tracing shows the to-and-fro flow across the pulmonary valve, with the signal below the line representing forward flow in systole (see ECG tracing for reference) and the signal above the line representing regurgitation during diastole.

erythrocytes. The speed and direction of blood flow in the line of the echo beam change the transducer's reference frequency. This frequency change can be translated into volumetric flow (L/min) data for estimating systemic or pulmonary blood flow and into pressure (mm Hg) data for estimating gradients across valves or across septal defects or vascular communications such as shunts. Color Doppler permits highly accurate assessment of the presence and direction of intracardiac shunts and allows identification of small or multiple left-to-right or right-to-left shunts (Fig. 472.22). The severity of valvular insufficiency can be evaluated qualitatively with both pulsed and color Doppler (Fig. 472.23). Alterations in venous Doppler flow patterns can be used to detect abnormalities of systemic and pulmonary veins, and alterations of atrioventricular valve Doppler flow patterns can be used to assess ventricular

diastolic functional abnormalities, particularly the **E/A ratio**, the ratio of peak velocity flow in diastole (i.e., the ratio of the early diastole E wave to the peak velocity flow in late diastole caused by atrial contraction).

M-mode, 2D, and Doppler echocardiographic methods of assessing LV systolic and diastolic function (e.g., end-systolic wall stress, dobutamine stress echocardiography, Doppler tissue imaging) have proved useful in the serial assessment of patients at risk for the development of both systolic and diastolic ventricular dysfunction and ventricular dyssynchrony (where the coordination of left and right ventricular contraction is abnormal). Such patients include those with cardiomyopathies, those receiving anthracycline drugs for cancer chemotherapy, those at risk for iron overload, and those being monitored for rejection or coronary artery disease after heart transplantation.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Real-time 3D echocardiographic reconstruction is most valuable for the detailed assessment of cardiac morphology (Fig. 472.24). Details of valve structure, the size and location of septal defects, abnormalities of the ventricular myocardium, and details of the great vessels, which may not be as readily apparent using 2D imaging, can often be appreciated on 3D echocardiography. Reconstruction of the view that the surgeon will encounter in the operating room makes this technique a valuable adjunct for preoperative imaging.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE is a sensitive imaging technique that produces a clearer view of smaller lesions such as vegetations in endocarditis, especially in larger patients. It is useful in visualizing posteriorly located structures such as the atria, aortic root, and atrioventricular valves. TEE is useful as an intraoperative technique for monitoring cardiac function during both cardiac and noncardiac surgery and for screening for residual cardiac defects after the patient is initially weaned from cardiopulmonary bypass but before being disconnected from the bypass circuit. This technique has been especially helpful in evaluating the degree of residual regurgitation or stenosis after valve repairs and in searching for small muscular VSDs that may have been missed during the closure of larger defects. It is always preferable to make the diagnosis of **excessive valve regurgitation** while the patient is still in the operating room, so that the repair can be revised or the valve replaced, rather than after surgery, when the patient is already in the postoperative care unit. However, hemodynamic measurements made while the chest is open and the patient is still under anesthesia may be different from those made under more normal conditions, as when the patient is ready to be discharged from the hospital.

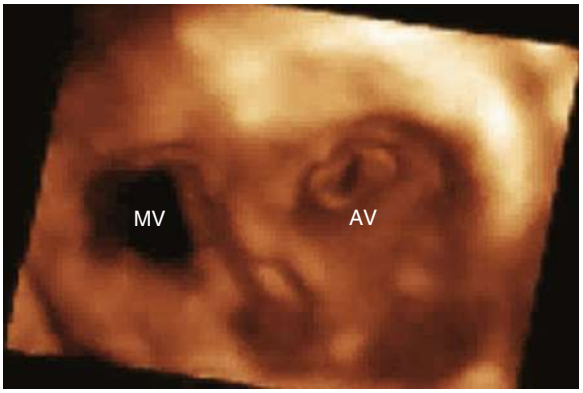

Fig. 472.24 Three-dimensional echocardiogram showing a short-axis view of the left ventricle. AV, Aortic valve; MV, mitral valve. *(Courtesy Dr. Norman Silverman, Stanford University, Stanford, CA.)*

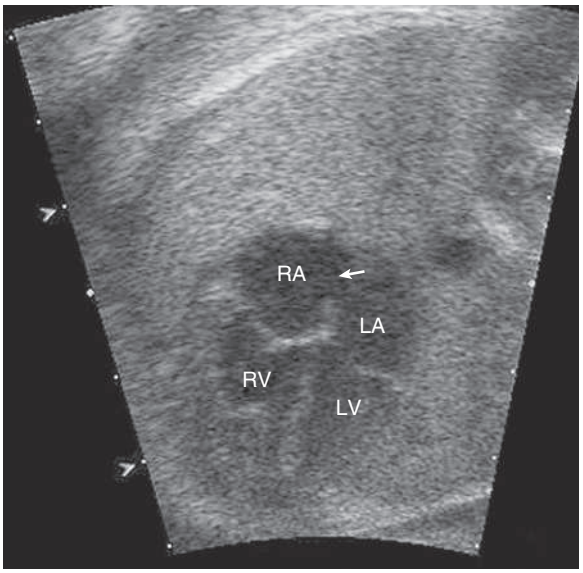

Fig. 472.25 Normal four-chamber view echocardiogram on a fetus at 20 wk of gestation. The foramen ovale *(arrow)* can be seen between the right and left atria. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

FETAL ECHOCARDIOGRAPHY

Fetal echocardiography can be used to evaluate cardiac structures and function or disturbances in cardiac rhythm (Fig. 472.25). Obstetricians may detect a possible heart defect when screening during routine obstetric ultrasonography (e.g., cardiac four-chamber view) or may refer the patient because of unexplained hydrops fetalis, a family history of CHD, or a maternal condition associated with fetal cardiac pathology, such as gestational diabetes, drug use, or infection. Fetal echocardiography can diagnose most significant congenital heart lesions as early as 17-19 weeks of gestation; accuracy at this early stage is limited, however, and families should understand that these studies cannot totally eliminate the possibility of CHD. Serial fetal echocardiograms have also demonstrated the importance of flow disturbance in the pathogenesis of CHD; such studies can show the intrauterine progression of a moderate lesion, such as aortic stenosis, into a more severe lesion, such as **hypoplastic left heart syndrome** (HLHS). M-mode echocardiography can diagnose rhythm disturbances in the fetus and can determine the success of antiarrhythmic therapy administered to the mother. A screening fetal echocardiogram is recommended for women with a previous child or first-degree relative with CHD, for those who are at higher risk of having a child with cardiac disease (e.g., insulin-dependent diabetes, women exposed to teratogenic drugs during early pregnancy), and in any fetus in whom a chromosomal abnormality is suspected or confirmed.

Early detection provides the opportunity to counsel and educate the parents about the severity of the cardiac lesion and potential therapeutic or palliative care options. Referral to a high-risk perinatal service is then performed for further ultrasound screening for associated anomalies of other organs and potential amniocentesis or sequencing of cell-free DNA in maternal blood for karyotyping. For fetuses with ductal dependent lesions, delivery can be planned at a tertiary care center, enhancing safety by avoiding the requirement for postnatal transport of an unstable infant. For fetuses with complex CHD at high risk for complications immediately at birth (e.g., HLHS with intact atrial septum), delivery can be arranged with an operating room and surgeon standing by. In utero treatment of CHD is an experimental procedure, with the most common procedure being aortic balloon valvuloplasty for HLHS.

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472.5 Exercise Testing

Daniel Bernstein

The normal cardiorespiratory system adapts to the extensive demands of exercise with a several-fold increase in oxygen consumption and cardiac output. Because of the large reserve capacity for exercise, significant abnormalities in cardiovascular performance may be present without symptoms at rest or during ordinary activities. When patients are evaluated in a resting state, significant abnormalities in cardiac function may not be appreciated, or if detected, their implications for quality of life may not be recognized. Permission for children with cardiovascular disease to participate in various forms of physical activity is frequently based on totally subjective criteria. As the importance of aerobic exercise is increasingly recognized, even for children with complex congenital heart lesions, exercise testing can provide a quantitative evaluation of the child's ability to participate safely in both competitive and noncompetitive sports. Exercise testing can also play an important role in evaluating symptoms and quantitating the severity of cardiac abnormalities. In children with coronary artery abnormalities (e.g., Kawasaki disease or COVID-19 with coronary aneurysms), exercise testing can detect ischemia that might otherwise be overlooked.

In older children, exercise studies are generally performed on a graded treadmill apparatus with timed intervals of increasing grade and speed. In younger children, exercise studies are often performed on a bicycle ergometer. Many laboratories have the capacity to measure both cardiac and pulmonary function noninvasively during exercise. This allows measurement of both resting and maximal oxygen consumption (Vo_{2max}) and the point at which anaerobic threshold is reached, which are important indicators of cardiovascular fitness.

As a child grows, the capacity for muscle work is enhanced with increased body size and skeletal muscle mass. All indices of cardiopulmonary function do not increase in a uniform manner. A major response to exercise is an increase in cardiac output, principally achieved through an increase in heart rate, but stroke volume (SV), systemic venous return, and pulse pressure are also increased. SVR is greatly decreased as the blood vessels in working muscle dilate in response to increasing metabolic demands. As the child becomes older and larger, the response of the heart rate to exercise remains prominent, but cardiac output increases because of growing cardiac volume capacity and thus SV. Responses to dynamic exercise are not dependent solely on age. For any given body surface area, boys have a larger SV than size-matched girls. This increase is also mediated by posture. Augmentation of SV with upright, dynamic exercise is facilitated by the pumping action of working muscles, which overcomes the static effect of gravity and increases systemic venous return.

Dynamic exercise testing defines not only endurance and exercise capacity but also the effect of such exercise on myocardial blood flow and cardiac rhythm. Significant ST segment depression or elevation reflects abnormalities in myocardial perfusion, such as might occur during exercise in children with extremely hypertrophied left ventricles. The **exercise ECG** is considered abnormal if the ST segment depression is >2 mm and extends for at least 0.06 seconds after the J point (onset of the ST segment) in conjunction with a horizontal-, upward-, or downward-sloping ST segment. A decrease in blood pressure before maximal exercise is reached is regarded as a risk indicator in patients with hypertrophic cardiomyopathy. Provocation of rhythm disturbances during an exercise study is an important method of evaluating select patients with known or suspected rhythm disorders. The effect of pharmacologic management can also be tested in this manner.

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472.6 Cardiac Imaging Studies

Daniel Bernstein

Magnetic resonance imaging (MRI) and **magnetic resonance angiography (MRA)** are extremely helpful in the diagnosis and management of patients with CHD and inflammatory lesions (Table 472.1). These techniques produce tomographic images of the heart in any projection (Fig. 472.26 and Fig. 472.27), with excellent contrast resolution of fat, myocardium, and lung, as well as moving blood from blood vessel walls. MRI is useful in evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.

MRA allows the acquisition of images in several tomographic planes. Within each plane, images are obtained at different phases of the cardiac cycle. Thus when displayed in a dynamic "cine" format, changes in wall thickening, chamber volume, and valve function can be displayed and analyzed. Blood flow velocity and blood flow volume can be calculated. MRA is an excellent technique for following patients serially after repair of complex CHD, such as tetralogy of Fallot. In these patients, MRA can be used to assess RV volume and mass and to quantify the amount of regurgitation through either the pulmonary or tricuspid valve. Other MRI techniques, such as myocardial delayed enhancement and tissue T1 weighting, can be used to quantify areas of myocardial scar in patients with cardiomyopathy or in patients after CHD repair, especially tetralogy of Fallot. **Magnetic resonance spectroscopy**, predominantly a research tool at present, provides a means of demonstrating relative concentrations of high-energy metabolites (adenosine triphosphate, adenosine diphosphate, inorganic phosphate, and phosphocreatine) within regions of the working myocardium.

Computer processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as *fly-through imaging.* These images allow the cardiologist to image the interiors of various cardiovascular structures (Fig. 472.28). These techniques are especially helpful in imaging complex peripheral arterial stenoses.

CT scanning can be used to perform rapid, respiration-gated cardiac imaging in children with resolutions down to 0.5 mm. Three-dimensional reconstruction of CT images is especially useful in evaluating branch pulmonary arteries, anomalies in systemic and pulmonary venous return, and great vessel anomalies such as coarctation of the aorta (Fig. 472.29).

Radionuclide angiography may be used to detect and quantify shunts and to analyze the distribution of blood flow to each lung. This technique is particularly useful in quantifying the volume of blood flow distribution between the two lungs in patients with abnormalities of the pulmonary vascular tree or to quantify the success of balloon angioplasty and intravascular stenting procedures. Gated blood pool scanning can be used to calculate hemodynamic measurements, quantify valvular regurgitation, and detect regional wall motion abnormalities. Thallium imaging can be performed to evaluate cardiac muscle perfusion. These methods can be used at the bedside of seriously ill children and can be performed serially, with minimal discomfort and low radiation exposure.

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472.7 Diagnostic and Interventional Cardiac Catheterization

Daniel Bernstein

The catheterization laboratory, once the site for initial diagnosis of CHD, has become the center of high-technology interventional procedures, allowing for the nonsurgical repair or palliation of heart defects that once required open heart surgery. Some centers have developed

Table 472.1 Cardiac MRI Assessment of Myocardial Inflammation

CAUSE	SPECIFIC CAUSE OF MECHANISM	KEY MRI FINDING
Infection	Infectious agents can induce cardiac injury by directly infecting cardiomyocytes or through cellular or humoral immune activation Viral: Enteroviruses, coronaviruses, adenoviruses, parvovirus B19, Herpesviridae 6, CMV, EBV, HIV, influenza; SARS-CoV-2 can infect cardiomyocytes by binding to the ACE2 receptor, although immune dysregulation is likely a more prominent mechanism of myocardial injury Bacterial: *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum,* group A streptococcus (likely postinfectious) Protozoal: *Trypanosoma cruzi* (Chagas disease), *Toxoplasma gondii* Parasitic: *Echinococcus granulosus, Trichinella spiralis*	**Viral myocarditis:** Linear subepicardial or midwall LGE, commonly involving the basal inferolateral wall, basal anterior septum, mid-inferolateral wall, and basal to mid-inferior wall, with corresponding T2 hyperintensity or high T2 **Chagas disease:** LGE present in up to 70% of patients, most commonly at the left ventricular apex, apical inferior and lateral wall, and basal to mid-inferolateral wall; LGE is usually midwall or subepicardial and, less commonly, subendocardial or transmural with apical aneurysms **Bacterial and parasitic myocarditis:** Limited data on MRI findings with no specific pattern **COVID-19:** Findings may be similar to non-COVID viral myocarditis, although some studies have indicated a higher prevalence of diffuse myocardial edema, with global elevation of T1 and T2 mapping values
Postvaccination	mRNA COVID-19 vaccines: Proposed mechanisms include immune activation and dysregulation and molecular mimicry between viral spike protein and an unknown cardiac protein	**mRNA COVID-19 vaccination:** There are currently limited MRI data, mostly from case series to date; MRI findings appear to be typical for viral myocarditis, although the severity and extent of MRI abnormalities reported have been relatively mild; axillary lymphadenopathy ipsilateral to the vaccination site may be present and may be a useful clue, particularly if a history of recent vaccine administration is not provided
Systemic disease	Several systemic diseases are associated with myocardial inflammation: Vasculitides: EGPA, Kawasaki disease Connective tissue disorders: Systemic sclerosis, SLE, rheumatoid arthritis, dermatomyositis Granulomatous disease: Sarcoidosis	**EGPA:** MRI findings include patchy midwall and subepicardial LGE with corresponding T2 hyperintensity and subendocardial apical LGE with or without apical thrombus; concomitant pulmonary opacities might be present **SLE:** Patchy or linear midwall and subepicardial LGE in one third of patients; elevated T1 and T2 value decrease after antiinflammatory treatment; higher prevalence of pericardial and pleural effusion and thickening than in other causes of myocarditis **Sarcoidosis**: Patchy and nodular LGE with associated high T2, most common at the basal septum and basal inferolateral segment; associated findings include mediastinal and hilar lymphadenopathy and pulmonary opacities
Drug related	Hypersensitivity reactions: Penicillin, cephalosporins, benzodiazepines, tricyclic antidepressants Toxic reactions: Anthracyclines, amphetamines, cyclophosphamide Immune activation or dysregulation: ICI-related myocarditis	**ICI-related myocarditis**: Diffusely elevated T1 and T2 values in 78% and 43% of patients, respectively; in one study, only 48% of patients met both T1 and T2 modified Lake Louise criteria; LGE present in 48% of patients, most commonly subepicardial or midmyocardial, and predominating in the basal and mid-inferior and inferolateral segments
Other	Hypereosinophilic syndrome, cocaine, postradiation injury, thyrotoxicosis, giant cell myocarditis	**Hypereosinophilic syndrome:** Similar MRI findings to EGPA, with higher prevalence of subendocardial LGE **Giant cell myocarditis:** MRI appearance is similar to cardiac sarcoidosis, although LGE tends to be more extensive and right ventricular involvement more common

ACE2, Angiotensin-converting enzyme 2; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EGPA, eosinophilic granulomatosis with polyangiitis; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; SLE, systemic lupus erythematosus.
From Sanchez Tijmes F, Thavendiranathan P, Udell JA, et al. Cardiac MRI assessment of nonischemic myocardial inflammation: state of the art review and update on myocarditis associated with COVID-19 vaccination. *Radiol Cardiothorac Imaging.* 2021;3(6):e210252, Table 1.

hybrid catheterization laboratories, combining standard fluoroscopic imaging with an operating suite, allowing combined approaches to treat complex congenital heart lesions.

DIAGNOSTIC CARDIAC CATHETERIZATION

Diagnostic catheterization is still performed (1) to assist in the initial diagnosis of some complex congenital heart lesions (e.g., tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, pulmonary atresia with intact ventricular septum and coronary sinusoids, HLHS with mitral stenosis); (2) in cases in which other imaging studies are equivocal; (3) in patients for whom hemodynamic assessment is critical (to determine the size of a left-to-right shunt in borderline cases or to determine the presence or absence of pulmonary vascular disease in an older patient with a left-to-right shunt); (4) between stages of repair of complex CHD (e.g., hypoplastic left or right heart syndromes); (5) for long-term surveillance of patients with complex CHD (e.g., after Fontan palliation for single ventricles); (6) for myocardial biopsy in the diagnosis of cardiomyopathy or in screening for cardiac rejection after cardiac transplantation; and (7) for electrophysiologic study in the evaluation of cardiac arrhythmias (see Chapter 484).

Cardiac catheterization should be performed with the patient in as close to a basal state as possible. Conscious sedation or low-level anesthesia is routine. If a deeper level of general anesthesia is required, careful choice of an anesthetic agent is warranted to avoid depression of cardiovascular function and subsequent distortion of the calculations of cardiac output, PVR and SVR, and shunt ratios.

Cardiac catheterization in critically ill infants with CHD should be performed in a center where a pediatric cardiovascular surgical team is available in the event that an operation is required immediately afterward. The complication rate of cardiac catheterization is greatest in critically ill infants; they must be studied in a thermally neutral

environment and monitored closely for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Catheterization may be limited to the right-sided cardiac structures, the left-sided structures, or both the right and left sides of the heart. The catheter is passed into the heart under fluoroscopic guidance through a percutaneous entry point in a femoral or jugular vein. In infants and in a number of older children, the left side of the heart can be accessed by passing the catheter across a patent foramen ovale to the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral artery or, if necessary, via a transatrial septal puncture. The catheter can also be manipulated through abnormal intracardiac defects (ASD, VSD). Blood samples are obtained for measuring oxygen saturation in each cardiac chamber or blood vessel, allowing the calculation of shunt volumes. Pressures are measured for gradients across septal defects or valves and for calculating valve areas. Radiopaque contrast is injected to delineate cardiac and vascular structures. A catheter with a thermosensor tip (Swan-Ganz catheter) can be used to measure cardiac output by thermodilution. Specialized catheters can be used to measure more sophisticated indices of cardiac function; those with pressure-transducer tips can measure the first derivative of LV pressure (dP/dt). Conductance catheters can be used to generate pressure-volume loops, from which indices of both contractility (end-systolic elastance) and relaxation can be

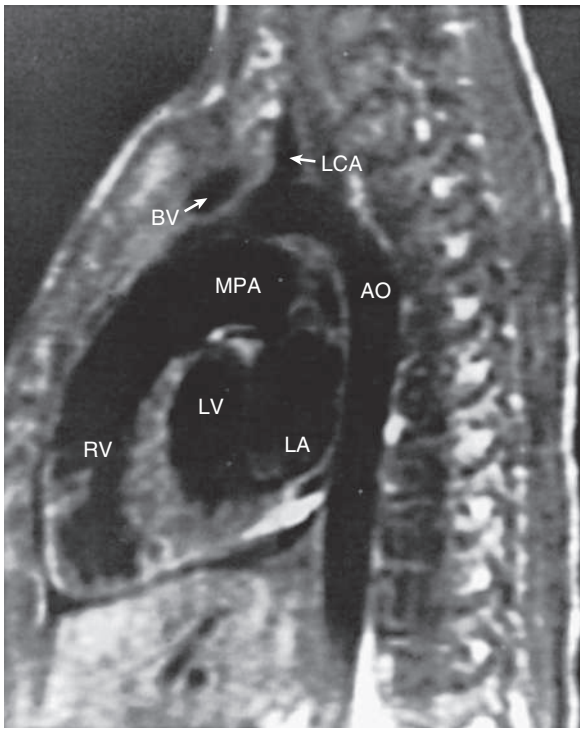

Fig. 472.26 Normal sagittal MRI. AO, Aorta; BV, brachiocephalic vein; LA, left atrium; LCA, left coronary artery; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle. *(From Bisset GS III. Cardiac and great vessel anatomy. In: El-Khoury GY, Bergman RA, Montgomery WJ, eds. Sectional Anatomy by MRI/CT. New York: Churchill Livingstone; 1990.)*

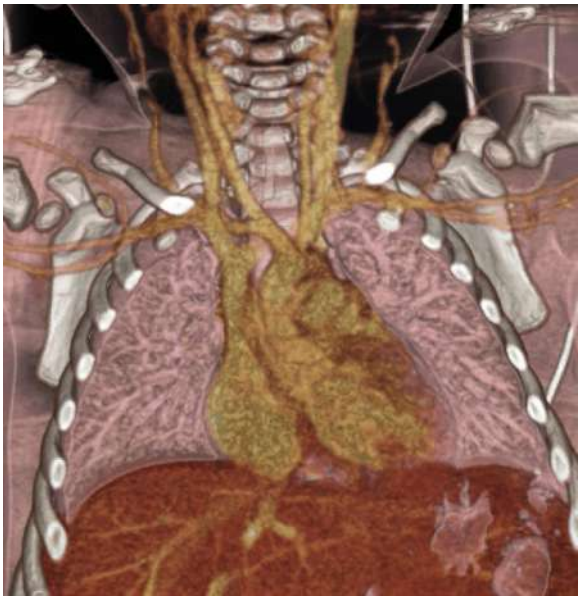

Fig. 472.28 Fly-through CT imaging in a patient with an aberrant right subclavian artery. Compression of the trachea by the aberrant artery can be visualized.

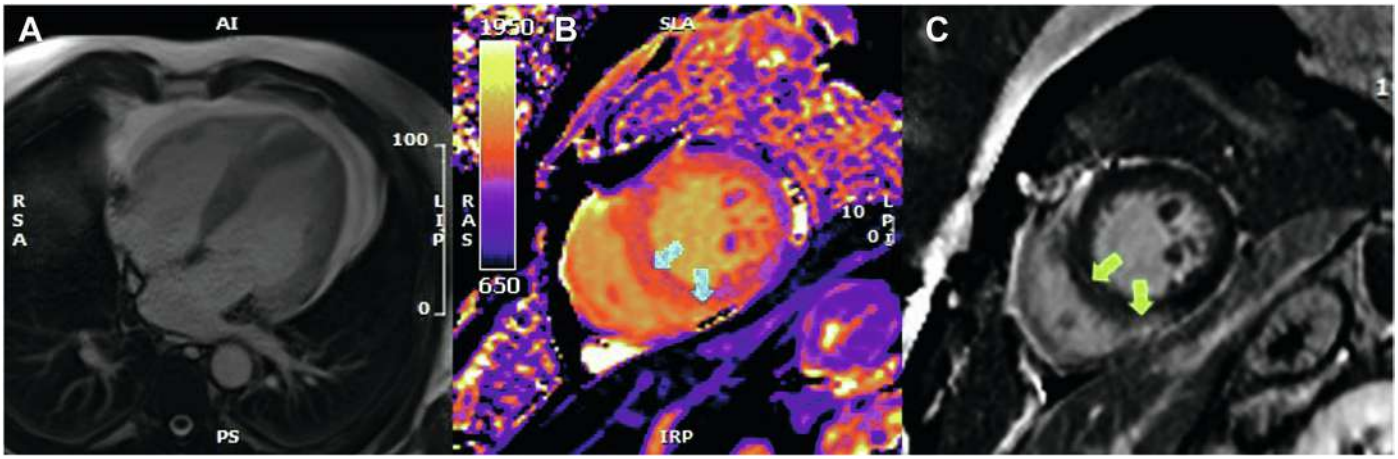

Fig 472.27 Cardiac magnetic resonance imaging (CMRI) findings in a patient with mRNA vaccine-associated myocarditis. Patient presented to hospital 2 days after the second COVID-19 mRNA vaccine with chest pain. Troponin T was elevated at 105 ng/L (normal < 15 ng/L). **A,** CMRI demonstrated normal left ventricular function. **B,** T1 mapping suggested myocardial edema in the inferoseptum and inferior segments (arrows) with corresponding nonischemic scar on late gadolinium enhancement imaging (**C,** *arrows*). *(From Crosier R, Kafil TS, Paterson DI. Imaging for Cardiovascular Complications of COVID-19: Cardiac Manifestations in Context. Can J Cardiol. 2023;39:779–792. Fig. 7.)*

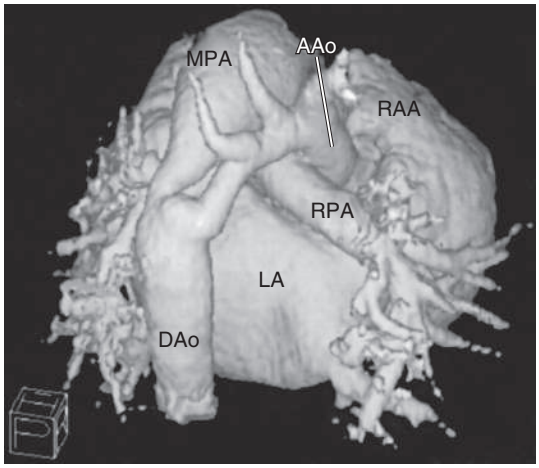

Fig. 472.29 Three-dimensional reconstruction of CT images from a neonate with severe coarctation of the aorta. The patent ductus arteriosus can be seen toward the left leading from the main pulmonary artery to the descending aorta. The tortuous and narrow coarctated segment is just to the right of the ductus. The transverse aorta is hypoplastic as well. AAo, Ascending aorta; DAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RAA, right atrial appendage; RPA, right pulmonary artery. *(Courtesy Dr. Paul Pitlick, Stanford University, Stanford, CA.)*

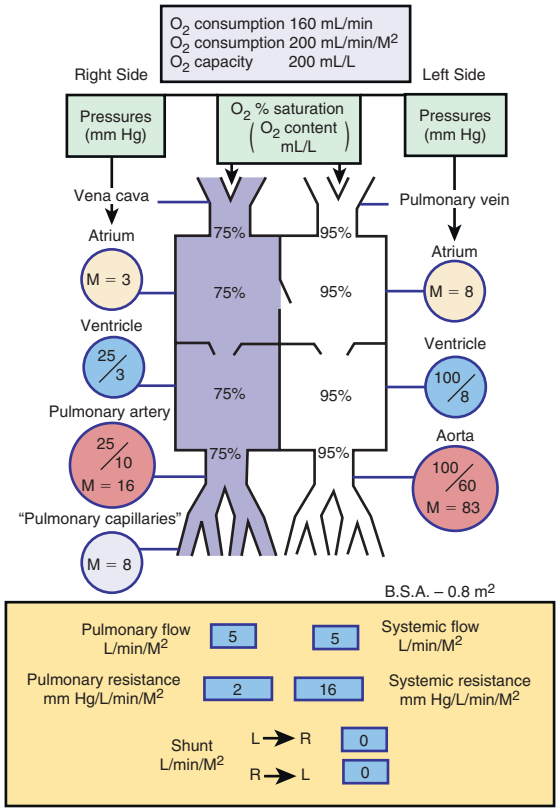

Fig. 472.30 Diagram of normal circulatory dynamics with pressure readings, oxygen content, and percent saturation. B.S.A., body surface area. *(Modified from Nadas AS, Fyler DC. Pediatric Cardiology, 3rd ed. Philadelphia: Saunders; 1972.)*

derived, although these are almost exclusively used in research studies. Complete hemodynamics can be calculated, including cardiac output, intracardiac left-to-right and right-to-left shunts, and SVR and PVR. Figure 472.30 depicts normal circulatory dynamics.

THERMODILUTION MEASUREMENT OF CARDIAC OUTPUT

The thermodilution method for measuring cardiac output is performed with a flow-directed, thermistor-tipped Swan-Ganz catheter. A known change in the heat content of the blood is induced at one point in the circulation (usually the right atrium or inferior vena cava) by injecting room-temperature saline, and the resultant change in temperature is detected at a point downstream (usually the pulmonary artery). This method is used to measure cardiac output in the catheterization laboratory in patients without shunts. Monitoring cardiac output by the thermodilution method can occasionally be useful in managing critically ill infants and children in an intensive care setting after cardiac surgery or in the presence of shock. In this case, a triple-lumen catheter is used for both cardiac output determination and measurement of pulmonary artery and pulmonary capillary wedge pressures.

ANGIOCARDIOGRAPHY

The major blood vessels and individual cardiac chambers may be visualized by selective injection of contrast material into specific chambers or great vessels. **Fluoroscopy** is used to visualize the catheter as it passes through the various heart chambers. After the cardiac catheter is properly placed in the chamber to be studied, contrast medium is injected with a power injector and cineangiograms are exposed. Modern catheterization labs use digital imaging technology, allowing for a significant reduction in radiation exposure. **Biplane cineangiocardiography** allows detailed evaluation of specific cardiac chambers and blood vessels in two planes simultaneously with the injection of a single bolus of contrast material. Various angled views (e.g., left anterior oblique, cranial angulation) are used to display specific anatomic features optimally in individual lesions.

Rapid injection of contrast medium under pressure into the circulation is not without risk, and each injection should be carefully planned. Contrast agents consist of hypertonic solutions, with some containing organic iodides, which can cause complications, including nausea, a generalized burning sensation, central nervous system symptoms, renal insufficiency, and allergic reactions. For patients with known renal insufficiency who require angiography, there are protocols to protect the kidneys involving prehydration and medications. Hypertonicity of the contrast medium may result in transient myocardial depression and a drop in blood pressure, followed soon afterward by tachycardia, an increase in cardiac output, and a shift of interstitial fluid into the circulation. This shift can transiently increase the symptoms of heart failure in critically ill patients.

INTERVENTIONAL CARDIAC CATHETERIZATION

Catheter treatment is the standard of practice for most cases of isolated pulmonary or aortic valve stenosis and for recoarctation of the aorta. A special catheter with a sausage-shaped balloon at the distal end is passed through the obstructed valve. Rapid filling of the balloon with a mixture of contrast material and saline solution results in tearing of the stenotic valve tissue, usually at the site of inappropriately fused raphe. Valvular pulmonary stenosis can be treated successfully by **balloon angioplasty**; in most patients, angioplasty has replaced surgical repair as the initial procedure of choice. The clinical results of this procedure are similar to those obtained by open heart surgery, but without the need for sternotomy or prolonged hospitalization. **Balloon valvuloplasty** for aortic stenosis has also yielded excellent results, although, as with surgery, aortic stenosis often recurs as the child grows, and multiple procedures may thus be required. One complication of both valvuloplasty and surgery is the creation of **valvular insufficiency**. This complication has more serious implications when it occurs on the aortic vs the pulmonary side of the circulation because regurgitation is less well tolerated at systemic arterial pressures.

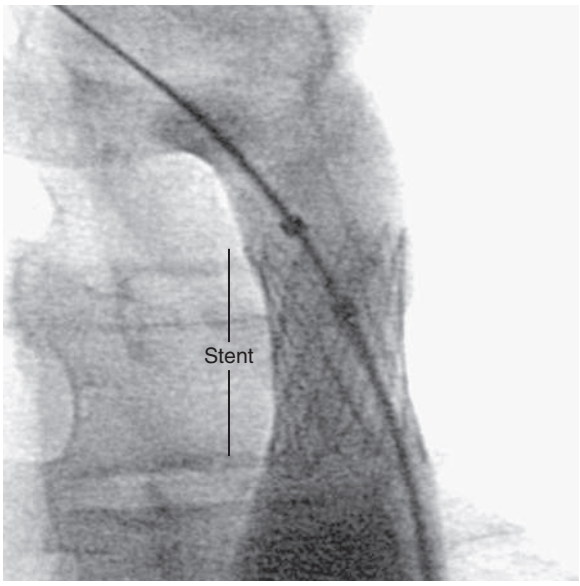

Fig. 472.31 Descending aortic angiogram showing intravascular stent placed in the descending aorta for treatment of recurrent coarctation of the aorta.

Balloon angioplasty is the procedure of choice for patients with restenosis of **coarctation of the aorta** after earlier surgery. It remains controversial whether angioplasty is the best procedure for native (unoperated) coarctation of the aorta in the infant because of greater recurrence risk and reports of late aneurysm formation, and most centers still refer primary coarctation in infants and young children for surgical repair. However, in older patients with previously undiagnosed coarctation, especially those with decreased LV function, primary angioplasty with stent placement may be considered. Other applications of the balloon angioplasty technique include amelioration of mitral stenosis, dilation of surgical conduits (e.g., RV-PA conduits), relief of branch pulmonary artery (PA) narrowing, dilation of systemic or pulmonary venous obstructions, and the pioneering balloon atrial septostomy **(Rashkind procedure)** for transposition of the great arteries (see Chapter 480.2).

Interventional catheterization techniques are being adapted for use in the fetus with lesions such as aortic stenosis to prevent their progression to more complex lesions such as HLHS. In these procedures, after administration of appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle (see Fig. 480.13). A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, it is hoped that normal LV growth potential is restored. Midterm results with this technique in a growing number of patients continue to show mixed results, with good ventricular growth leading to a two-ventricle circulation in approximately 25% of highly preselected patients.

In patients with branch pulmonary artery stenoses, **intravascular stents** are delivered over a balloon catheter and expanded within the vessel lumen (Fig. 472.31). Once placed, the stents can often be dilated to successively greater sizes as the patient grows, although their use in younger infants and children is limited by the extent they can be further expanded.

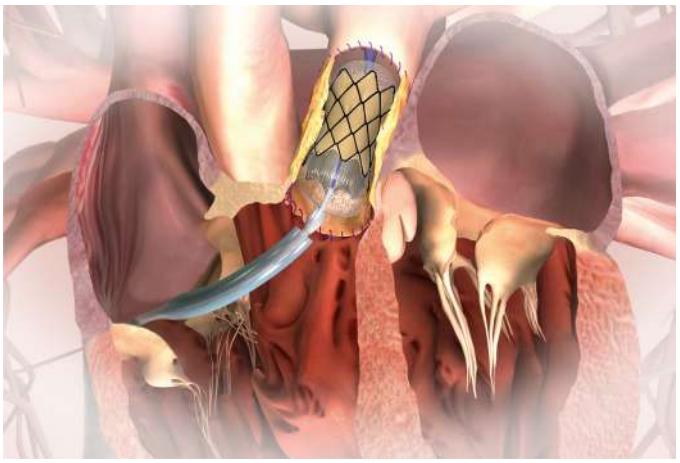

Fig. 472.32 Illustration of implantation of a Melody stent-valve delivered to the pulmonary position by a catheter inserted into the right femoral vein. *(Copyright Medtronic 2017, used with permission.)*

Closure of a small patent ductus arteriosus (PDA) is routinely achieved with catheter-delivered **coils** (see Fig. 475.11), whereas a larger PDA can be closed with a variety of sandwich-type devices. Closure of anomalous vascular connections (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils. Secundum ASDs are now routinely closed with a double disk occluder (e.g., **Amplatzer**) device (see Fig. 475.3). Versions of these devices are currently in clinical trials for closure of surgically difficult-to-reach muscular VSDs and for the more common perimembranous VSD. Catheter-delivered devices may also be used as an adjunct to complex surgical repairs (e.g., dilation or stenting of branch pulmonary artery or pulmonary vein stenosis). High-risk patients undergoing the Fontan operation (see Fig. 479.9) often have a small fenestration created between the right and left sides of the circulation to serve as a "pop-off valve" for high right-sided pressure in the early surgical period. Patients with these "fenestrated Fontans" are usually candidates for subsequent closure of the fenestration with a catheter-delivered device.

One of the greatest advances in interventional catheterization over the past decade has been **transcatheter valve implantation**. Typically, a porcine valve is sewn into an expandable stent (commercially available), which is then collapsed around a balloon catheter. The device is positioned across a stenotic or insufficient pulmonary or aortic valve and the balloon inflated, expanding both the stent and the tissue valve. The balloon catheter is then removed, leaving the new valve in place, well anchored by the stent to the walls of the main pulmonary artery or aorta. At this time, the most common application in children is replacement of the **pulmonary valve** (Melody or Harmony Valve) in patients who have had prior surgery for tetralogy of Fallot (usually because of residual pulmonary insufficiency) (Fig. 472.32). In older adults, the most common application is replacement of a stenotic aortic valve (transcatheter aortic valve replacement or TAVR). Stent valves have even been placed in the tricuspid position in children with tricuspid insufficiency. For older patients with mitral and tricuspid valve insufficiency, a clip device (Mitraclip) can be delivered by catheter to create a double-orifice valve, reducing the amount of insufficiency.

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Section 3

Congenital Heart Disease

Chapter 473

Epidemiology and Genetic Basis of Congenital Heart Disease

Daniel Bernstein

Congenital heart disease (CHD) occurs in approximately 0.6–1.3% of live births. The incidence is higher in stillborns (3–4%), spontaneous abortuses (10–25%), and premature infants (approximately 2%, excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valve (present in 1–2% of adults). Congenital cardiac defects have a wide spectrum of severity in infants: approximately 2-3 in 1,000 newborn infants will be symptomatic with heart disease in the first year of life. The diagnosis is established by 1 week of age in 40–50% of patients with CHD and by 1 month of age in 50–60%. Approximately 13% of infants with CHD have associated extracardiac malformations. With advances in both corrective and palliative surgery, 90% of children with CHD survive to adulthood, and in the United States, there are more adults living with CHD than there are children with CHD. Despite these advances, CHD remains the leading cause of death in children with congenital malformations. When patients with repaired or palliated CHD reach older adulthood, the risk of morbidity and mortality begins to increase (see Chapter 483.1). Table 473.1 summarizes the relative frequency of the most common congenital cardiac lesions.

Most congenital defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe cardiac defects, such as **hypoplastic left heart syndrome (HLHS)**, can usually be well compensated for by the fetal circulation. In HLHS the entire fetal cardiac output is ejected by the right ventricle via the ductus arteriosus into both the descending and ascending aortae (the latter filling in a retrograde fashion), so that fetal organ blood flow is minimally perturbed. Because the placenta provides for gas exchange and the normal fetal circulation has mixing between more highly and more poorly oxygenated blood at the foramen ovale and ductus arteriosus, fetal organ oxygen delivery is also not dramatically affected. It is only after birth, when the fetal pathways begin to close and the umbilical cord is cut, that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most frequently of the tricuspid valve. In these lesions, such as **Ebstein anomaly** of the tricuspid valve or severe right ventricular outflow obstruction (see Chapter 479.7), the parallel fetal circulation cannot compensate for the severe volume or pressure load imposed on the right side of the heart. In utero heart failure, often with fetal pleural and pericardial effusions, and generalized ascites **(nonimmune hydrops fetalis)** may occur.

Although the most significant transitions in the circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. When pulmonary vascular resistance (PVR) falls in the first several weeks of life, left-to-right shunting through intracardiac defects increases and symptoms and signs become more apparent. Thus in patients with a **ventricular septal defect (VSD)**, heart failure is often first noticed between 1 and 3 months of age (see Chapter 475.6) and not in the immediate newborn period. The severity of various defects can also change dramatically with growth; some VSDs may become smaller and even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be only moderate in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth (see Chapter 476.5). The physician should always be alert for associated noncardiac congenital malformations, which can adversely affect the patient's prognosis (Tables 473.2 and 473.3). Developmental delay of various degrees is also a concern in many patients with CHD and may have its origins in alterations in fetal blood flow patterns caused by the heart defect, postnatal hypoxemia, and the effects of cardiopulmonary bypass during open heart surgery.

ETIOLOGY

The cause of most congenital heart defects is still unknown. Many cases of CHD are multifactorial and may result from a combination of **genetic** predisposition and an as-yet-to-be-determined **environmental** stimulus. Overall, variants in approximately 400 genes have been identified as potentially causative of CHD. Despite these advances, half of cases still lack a known genetic cause. A small percentage of congenital heart lesions are related to known chromosomal abnormalities, in particular, trisomies 21, 13, and 18 and Turner syndrome; heart disease is found in >90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome (see Table 473.3). Ethnic factors may have a role in CHD; certain types of VSDs (supracristal) are more common in Asian children. There are also male:female differences for many common forms of CHD. The risk of CHD increases if a first-degree relative (parent or sibling) is affected, again emphasizing the role of genetics, even if the individual genes have not yet been identified.

A growing list of congenital heart lesions has been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects (see Table 473.3 and Table 473.4). **Fluorescence**

Table 473.1 Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35–30
Atrial septal defect (secundum)	6–8
Patent ductus arteriosus	6–8
Coarctation of aorta	5–7
Tetralogy of Fallot	5–7
Pulmonary valve stenosis	5–7
Aortic valve stenosis	4–7
D-Transposition of great arteries	3–5
Hypoplastic left ventricle	1–3
Hypoplastic right ventricle	1–3
Truncus arteriosus	1–2
Total anomalous pulmonary venous return	1–2
Tricuspid atresia	1–2
Single ventricle	1–2
Double-outlet right ventricle	1–2
Others	5–10

*Excluding patent ductus arteriosus in preterm neonates, bicuspid aortic valve, physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

Table 473.2 Genes and Loci Associated with Congenital Heart Disease

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Alagille	*JAG 1* *NOTCH2*	20p12.2 1p12-p11	PPS, TOF, PA	>90	Bile duct paucity, posterior embryotoxon, butterfly vertebrae, renal defects
CFC	*BRAF* *KRAS* *MAP2K1* *MAP2K2*	7q34 12p12.1 15q22.31 19p13.3	PVS, ASD, HCM	75	Curly hair, sparse eyebrows, feeding problems, developmental delay, intellectual disability
Cantu	*ABCC9*	12p12.1	PDA, BAV, HCM, CoA, PE, AS	75	Hypertrichosis at birth, macrocephaly, narrow thorax, coarse facies, macroglossia, broad hands, advanced bone age
Char	*TFAP2B*	6p12.3	PDA, VSD	58	Wide-set eyes, down-slanting palpebral fissures, thick lips, hand anomalies
CHARGE	*CHD7*	8q12	TOF, PDA, DORV, AVSD, VSD	75–85	Coloboma, choanal atresia, genital hypoplasia, ear anomalies, hearing loss, developmental delay, poor growth, intellectual disability
Costello	*HRAS*	11p15.5	PVS, ASD, VSD, HCM, arrhythmias	44–52	Short stature, feeding problems, broad facies, bitemporal narrowing, redundant skin, intellectual disability
22q11.2DS	*TBX1*	22q11.2 deletion	Conotruncal defects, VSD, IAA, ASD, VR	74–85	Cleft palate, bifid uvula, velopharyngeal insufficiency, microcephaly, hypocalcemia, immune deficit, psychiatric disorder, learning disability
Ellis-van Creveld	*EVC* *EVC2*	4p16.2 4p16.2	Common atrium	60	Skeletal dysplasia, short limbs, polydactyly, short ribs, dysplastic nails, respiratory insufficiency
Holt-Oram	*TBX5*	12q24.1	VSD, ASD, AVSD, conduction defects	50	Absent, hypoplastic, or triphalangeal thumbs; phocomelia; defects of radius; limb defects more prominent on left
Kabuki	*KMT2D* *KDM6A*	12q13 Xp11.3	CoA, BAV, VSD, TOF, TGA, HLHS	50	Growth deficiency, wide palpebral fissures, large protuberant ears, fetal finger pads, intellectual disability, clinodactyly
Noonan	*PTPN11* *SOS1* *RAF1* *KRAS* *NRAS* *RIT1* *SHOC2* *SOS2* *BRAF*	12q24.13 2p22.1 3p25.2 12p12.1 1p13.2 1q22 10q25.2 14q21.3 7q34	Dysplastic PVS, ASD, TOF, AVSD, HCM, VSD, PDA	75	Short stature, hypertelorism, down-slanting palpebral fissures, ptosis, low posterior hairline, pectus deformity, bleeding disorder, chylothorax, cryptorchidism
VACTERL association	Unknown		VSD, ASD, HLHS, PDA, TGA, TOF, TA	53–80	Vertebral anomalies, anal atresia, tracheoesophageal fistula, renal anomalies, radial dysplasia, thumb hypoplasia, single umbilical artery
Williams-Beuren	7q11.23 deletion (*ELN*)	7q11.23	SVAS, PAS, VSD, ASD	80	Unusual facies, thick lips, strabismus, stellate iris pattern, intellectual disability
Carpenter	*RAB23*	6p11.2	VSD, ASD, PDA, PS, TOF, TGA	50	Craniosynostosis, brachydactyly, syndactyly, polydactyly, obesity

Table 473.2 Genes and Loci Associated with Congenital Heart Disease—cont'd

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Coffin-Siris	*ARID1B* *SMARCB1* *ARID1A* *SMARCB1* *SMARCA4* *SMARCE1*	6q25 22q11 1p36.1 22q11.23 19p13.2 17q21.2	ASD, AVSD, VSD, MR, PDA, PS, DEX, AS	20–44	Developmental delay, coarse facies, hypoplastic distal phalanges, short stature, intellectual disability
Cornelia de Lange	*NIPBL* *SMC1L1* *SMC3*	5p13 Xp11.22 10q25	PVS, VSD, ASD, PDA	33	Microbrachycephaly, synophrys, arching eyebrows, growth retardation, intellectual disability, micromelia
Goldenhar	Unknown		VSD, PDA, TOF, CoA, conotruncal defects	32	Hemifacial microsomia, epibulbar dermoids, microtia, hemivertebrae
Mowat-Wilson	*ZEB2*	2q22.3	VSD, CoA, ASD, PDA, PAS	54	Short stature, microcephaly, Hirschsprung disease, intellectual disability, seizures
Rubinstein-Taybi	*CBP* *EP300*	16p13.3 22q13.2	PDA, VSD, ASD, HLHS, BAV	33	Microcephaly, growth retardation, down-slanting palpebral fissures, low-set malformed ears, prominent or beaked nose, intellectual disability, broad thumbs and toes
Smith-Lemli-Opitz	*DHCR7*	11q12-13	AVSD, HLHS, ASD, PDA, VSD	50	Microcephaly, ptosis, genital anomalies, renal anomalies, broad nasal tip with anteverted nostrils, intellectual disability, syndactyly
Adams-Oliver	*ARHGAP31* *DOCK6* *RBPJ* *EOGT* *NOTCH1* *DLL4*	3q13 19p13.2 4p15.2 3p14.1 9q34.3 15q15.1	ASD, VSD, CoA, HLHS, DORV	20	Aplasia cutis congenita, terminal transverse defects of hands, fingers, toes, feet
Baller-Gerold	*RECQL4*	8q24.3	VSD, TOF, subaortic disease	25	Craniosynostosis, micrognathia, small mouth, radial aplasia/hypoplasia, imperforate anus, renal anomalies
Beckwith-Wiedemann	*CDKNIC*	11p15.4	VSD, HLHS, PS	6.5	Macrosomia, macroglossia, omphalocele, risk of malignancy
Coffin-Lowry	*RSK2*	Xp22.2	LVNC, MVP, AVA	5–14	Growth deficiency, coarse facies, everted lower lip, hypodontia, intellectual disability
Duane-radial ray (Okihiro)	*SALL4*	20q13.2	ASD, PVS, VSD	<10	Unilateral or bilateral Duane anomaly, hypoplasia of thumbs, hypoplastic radius and ulna, renal malformations, ear anomalies
Fragile X	*FMR1*	Xq27.3	MVP, aortic dilation	<10	Macrocephaly, intellectual disability, hand flapping, speech abnormality, autism spectrum disorder, macroorchidism, seizures, prominent forehead, large ears
Nance-Horan	*NHS*	Xp22.13	TOF, VSD, PDA	<10	Congenital cataracts, strabismus, peg-shaped supernumerary teeth, other dental anomalies, prominent ears, brachymetacarpalia

Continued

Table 473.2 Genes and Loci Associated with Congenital Heart Disease—cont'd

SYNDROME	GENE(S)	LOCI	CARDIAC DISEASE	CONGENITAL HD (%)	OTHER CLINICAL FINDINGS
Peter's Plus	*B3GALTL*	13q12.3	ASD, VSD, PVS, BPV, subvalvular AS	<30	Short limb growth deficiency, intellectual disability, autism spectrum disorder, prominent forehead, cupid's bow upper lip, cleft lip ± cleft palate, Peter's anomaly, cataracts, hydronephrosis
Roberts	*ESC02*	8p21.1	ASD, AS	<20	Growth deficiency of prenatal onset, cleft lip ± cleft palate, hypertelorism, sparse hair, hypomelia with variable limb reduction defects, cryptorchidism
Robinow	*RDR2 (AR)* *WNT5A (AD)*	9q22	RVOTO	29 AD 13 AR	Macrocephaly, frontal bossing, prominent eyes, small upturned nose, short forearms, hemivertebrae, hypoplastic phalanges of hands and toes, hypoplastic genitalia
Saethre-Chotzen	*TWIST*	7p21p22	VSD	<10	Craniosynostosis, brachycephaly, high flat forehead, hypertelorism, ptosis, partial cutaneous syndactyly, broad great toes, strabismus
Short rib polydactyly type I	*DYNC2H1*	11q22.3	TGA, DORV, DOLV, AVSD, HRH	<25	Short stature, postaxial polydactyly of hands or feet, short horizontal ribs, small iliac bones, polycystic kidneys, early death from respiratory insufficiency
Simpson-Golabi-Behmel	*GPC3*	Xq26.2	TGA, VSD, PVS, CoA, AS, PDA, BAV, CM	26	Macrosomia, coarse face, macroglossia, hepatosplenomegaly, nephromegaly, variable cognitive disability
Sotos	*NSD1*	5q35.3	ASD, PDA, VSD	21	Excessive size, large hands and feet, prominent forehead, hypotonia, variable intellectual disability, scoliosis, advanced bone age
Townes-Brocks	*SALL1*	16p12.1	ASD, TOF, VSD, TA, PA, PDA	14–25	Auricular anomalies, preauricular tags, hearing loss, thumb hypoplasia/polydactyly, imperforate anus, renal agenesis, multicystic kidney, microphthalmia

22q11.2DS, 22q11.2 deletion syndrome; AD, autosomal dominant; AR, autosomal recessive; AS, aortic stenosis; ASD, atrial septal defect; AVA, aortic valve anomaly; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; CFC, cardiofaciocutaneous; CHARGE, coloboma, heart defects, choanal atresia, retarded growth and development, genital anomalies, and ear anomalies; CM, cardiomyopathy; CoA, coarctation of the aorta; DEX, dextrocardia; DOLV, double-outlet left ventricle; DORV, double-outlet right ventricle; HCM, hypertrophic cardiomyopathy; HD, heart disease; HLHS, hypoplastic left heart; HRH, hypoplastic right heart; IAA, interruption of aortic arch; LVNC, left ventricular noncompaction; MR, mitral regurgitation; MVP, mitral valve prolapse; PA, pulmonary atresia; PAS, pulmonary artery stenosis; PDA, patent ductus arteriosus; PE, pericardial effusion; PPS, peripheral pulmonary stenosis; PS, pulmonary stenosis; PVS, pulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; SVAS, supravalvular aortic stenosis; TA, truncus arteriosus; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VACTERL, association of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal and limb anomalies; VR, vascular ring; VSD, ventricular septal defect.

From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 5.

in situ hybridization (FISH) analysis allows rapid screening of suspected cases if a specific chromosomal abnormality is suspected. Chromosome microarray tools, including **array comparative genome hybridization** and **single nucleotide polymorphism (SNP) arrays**, have identified copy number variations (microdeletions or microduplications) or SNPs in many patients with CHD and suspicion of a congenital anomaly syndrome. These variants are submicroscopic and thus not visible on routine chromosome analysis. Comparative genome hybridization has in many cases replaced routine karyotyping in the clinical workup of newborns with CHD. Overall, 25% of cases of CHD can be associated with a gene alteration using these methodologies. Whole exome and whole genome sequencing are available for clinical genetic evaluations. The advantage of whole genome sequencing is that it allows the assessment of noncoding DNA sequences, which could participate in the regulation of gene expression of cardiac developmental gene pathways (Table 473.5).

A well-characterized genetic cause of CHD is the deletion of a large region (1.5-3 Mb) of chromosome 22q11.2, known as the **DiGeorge**

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
I. ANEUPLOIDES (IDENTIFIABLE BY ROUTINE KARYOTYPE)			
Trisomy 8 mosaicism	Widely spaced eyes, broad nasal bridge, small jaw, high arched palate, cryptorchidism, renal anomalies, skeletal/vertebral anomalies	25	VSD, PDA, CoA, PVS, TAPVR, TrA
Trisomy 9/mosaicism	Prenatal and postnatal growth restriction, microcephaly, deep-set eyes, low-set ears, severe intellectual disability	65	PDA, LSVC, VSD, TOF/PA, DORV
Trisomy 13 (Patau syndrome)	Cleft lip and palate, scalp defects, hypotelorism, microphthalmia or anophthalmia, colobomata of irides, holoprosencephaly, microcephaly, deafness, severe intellectual disability, rib abnormalities, polydactyly, omphalocele, renal abnormalities, hypospadias, cryptorchidism, uterine abnormalities	57–80	ASD, VSD, PDA, HLHS, laterality defects, atrial isomerism
Trisomy 18 (Edwards syndrome)	IUGR, polyhydramnios, micrognathia, short sternum, hypertonia, rocker-bottom feet, overlapping fingers and toes, TEF, CDH, omphalocele, renal anomalies, biliary atresia, severe intellectual disability	80–90	ASD, VSD, PDA, TOF, DORV, TGA, CoA, BAV, BPV, polyvalvular nodular dysplasia
Trisomy 21 (Down syndrome)	Hypotonia, hyperextensibility, epicanthal folds, up-slanting palpebral fissures, single palmar transverse crease, clinodactyly of fifth finger, brachydactyly, variable intellectual disability, premature aging	40–50	AVSD, VSD, ASD, (TOF, TGA less common)
Monosomy X (Turner syndrome, 45,X)	Lymphedema of hands and feet, widely spaced hypoplastic nipples, webbed neck, primary amenorrhea, short stature, normal intelligence, or mild learning disability	23–35	CoA, BAV, AS, HLHS, aortic dissection
II. CHROMOSOME ABNORMALITIES (IDENTIFIABLE ON KARYOTYPE AND CHROMOSOMAL MICROARRAY)			
3p25 deletion	Prenatal and postnatal growth deficiency, polydactyly, microcephaly, intellectual disability, renal anomalies	33	VSD, AVSD, tricuspid atresia
Deletion 4p16.3 (Wolf-Hirschhorn syndrome)	Microcephaly, widely spaced eyes, broad nasal bridge (Greek helmet appearance), downturned mouth, micrognathia, preauricular skin tags, severe intellectual disability, seizures, poor growth	50–65	ASD, VSD, PDA, LSVC, aortic atresia, dextrocardia, TOF, tricuspid atresia
Deletion 4q	Growth restriction, intellectual disability, cleft palate, broad nasal bridge, micrognathia, abnormal ears, genitourinary defects	50	VSD, PDA, AS, ASD, TOF, CoA
Deletion 5p (cri-du-chat)	Catlike cry, prenatal and postnatal growth restriction, round face, widely spaced eyes, epicanthal folds, single palmar transverse crease, severe intellectual disability	30–60	VSD, ASD, PDA
Deletion 9p syndrome	Craniosynostosis, trigonocephaly, up-slanting palpebral fissures, abnormal ear pinnae, scoliosis, micropenis, cryptorchidism, intellectual disability	35–50	VSD, PDA, PVS
Deletion 10p	Frontal bossing, short down-slanting palpebral fissures, small low-set ears, micrognathia, cleft palate, short neck, urinary/genital and upper-limb anomalies	42	BAV, ASD, VSD, PDA, PVS, CoA
Duplication 10q24-qter	Prenatal growth restriction, intellectual disability, camptodactyly, renal anomalies, cryptorchidism	50	AVSD, VSD
III. COPY NUMBER VARIANTS (IDENTIFIABLE BY CHROMOSOMAL MICROARRY)			
1p36 deletion	Growth deficiency, intellectual disability, microcephaly, deep-set eyes, low-set ears, hearing loss, hypotonia, seizures, CNS defects, genital anomalies	70	PDA, VSD, ASD, BAV, Ebstein anomaly, noncompaction cardiomyopathy

Continued

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease—cont'd

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
1q21.1 deletion	Short stature, microcephaly, colobomas, microphthalmia, hearing loss, seizures, mild intellectual disability, autism spectrum disorder, skeletal malformations	N/A	PDA, VSD, ASD, TrA, TOF
1q21.1 duplication	Large head size, hemivertebrae, variable intellectual disability, variable autistic features, hypospadias, clubfoot	N/A	TOF, TGA, PVS
1q41q42 microdeletion	Growth restriction, intellectual disability, microcephaly, diaphragmatic hernia, seizures, short limbs	40	BAV, ASD, VSD, TGA
1q43q44 microdeletion	Prenatal and postnatal poor growth, intellectual disability, limited speech, microcephaly, deep-set eyes, microcephaly, large low-set ears, cleft palate, agenesis of corpus callosum	N/A	VSD, CoA, HLHS
2q31.1 microdeletion	Prenatal and postnatal poor growth, large ventricles, microcephaly, narrow forehead, down-slanting palpebral fissures, cleft palate/cleft lip, limb defects, hypoplastic genitalia	25	VSD, ASD, PDA
2q37 microdeletion	Short stature, obesity, intellectual disability, sparse hair, arched eyebrows, epicanthal folds, thin upper lip, small hands and feet, clinodactyly	30	VSD, ASD, CoA, hypoplastic aortic arch
Deletion 7q11.23 (Williams-Beuren syndrome)	Infantile hypercalcemia, skeletal and renal anomalies, cognitive deficits, "social" personality, elfin facies	53–85	Supravalvar AS and PS, PPS
8p23.1 deletion	Microcephaly, poor growth, deep-set eyes, malformed ears, small chin, genital anomalies in males, intellectual disability	50–75	AVSD, PVS, VSD, TOF
9q34.3 Subtelomeric deletion (Kleefstra syndrome)	Short stature, obesity, intellectual disability, microcephaly, behavior abnormalities, brain anomalies, hypertelorism, arched eyebrows, midface hypoplasia	31–44	ASD, VSD, TOF, pulmonary arterial stenosis
Deletion 11q (Jacobsen syndrome)	Growth restriction, developmental delay, thrombocytopenia, platelet dysfunction, widely spaced eyes, strabismus, broad nasal bridge, thin upper lip, prominent forehead, intellectual disability	56	HLHS, AS, VSD, CoA, Shone complex
15q24 microdeletion	Prenatal and postnatal growth restriction, intellectual disability, abnormal corpus callosum, microcephaly, high forehead, down-slanting palpebral fissures, tapered eyebrows, abnormal ear pinnae, hearing loss, hypospadias, scoliosis, coloboma, strabismus	40	PDA, pulmonary arterial stenosis, PVS
16p11.2p12.2 microdeletion	Hypotonia, intellectual disability, long narrow face, deep-set eyes, low-set malformed ears	33	TOF, BAV, pulmonary atresia
17q21 microdeletion	Abnormal hair pigmentation, up-slanting palpebral fissures, epicanthal folds, bulbous nasal tip, strabismus, ptosis, long slender fingers, hip dislocation, renal anomalies, spine deformities, cryptorchidism, global developmental delay	27	PVS, ASD, VSD, BAV
Deletion 20p12 (Alagille syndrome)	Bile duct paucity, cholestasis, skeletal or ocular anomalies, broad forehead, widely spaced eyes, underdeveloped mandible	85–94	Peripheral PA hypoplasia, TOF, PVS (left-sided heart lesions and septal defects less common)
22q11.2DS (DiGeorge, velocardiofacial, and conotruncal anomaly face syndrome)	Hypertelorism, micrognathia, low-set posteriorly rotated ears, thymic and parathyroid hypoplasia, hypocalcemia, feeding/speech/learning/behavioral disorders, immunodeficiency, palate/skeletal/renal anomalies, learning disability	75	IAA-B, TrA, isolated aortic arch anomalies, TOF, conoventricular VSD

Table 473.3 Chromosomal Aneuploidies and Copy Number Variants Associated with Congenital Heart Disease—cont'd

CHROMOSOME CHANGE	MAIN FEATURES	PERCENT WITH CONGENITAL HD	HEART ANOMALY
22q11.2 duplication	Very variable phenotype, some with velopharyngeal insufficiency, cleft palate, hearing loss, minor facial anomalies, mild learning disability to normal learning ability, hypotonia, scoliosis, frequent infections	15	TOF, HLHS, VSD, PVS, TrA
22q13 microdeletion (Phelan-McDermid syndrome)	Normal growth, intellectual disability, dolichocephaly, dysplastic ears, pointed chin, large fleshy hands, hypotonia	>25	PDA, VSD, ASD, TAPVR

22q11.2DS, 22q11.2 deletion syndrome; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BPV, bicuspid pulmonary valve; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HD, heart disease; HLHS, hypoplastic left heart syndrome; IAA-B, interrupted aortic arch type B; IUGR, intrauterine growth retardation; LSVC, persistent left superior vena cava; N/A, not available; PA, pulmonary artery; PDA, patent ductus arteriosus; PPS, peripheral pulmonary stenosis; PS, pulmonary stenosis; PVS, pulmonic valve stenosis; TAPVR, total anomalous pulmonary venous return; TEF, tracheoesophageal fistula; TGA, D-transposition of the great arteries; TOF, tetralogy of Fallot; TOF/PA, tetralogy of Fallot with pulmonary atresia; TrA, truncus arteriosus; VSD, ventricular septal defect.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Appendix Table.

Table 473.4 Disease Genes for Nonsyndromic Congenital Cardiovascular Disease

GENE	CARDIOVASCULAR MALFORMATION	NONSYNDROMIC (NS) OR SYNDROMIC (S)
TRANSCRIPTION FACTORS		
CITED2	ASD, VSD	NS
GATA4	ASD, VSD, AVSD, PVS, TOF	NS
GATA6	PTA, TOF	NS
MED13L	TGA	NS
NR2F2	AVSD, AS, CoA, VSD, HLHS, TOF	NS
NKX2-5	ASD, atrioventricular conduction delay, TOF, HLHS	NS
NKX2.6	PTA	NS
TBX20	ASD, VSD, MS, DCM	NS
ZFPM2/FOG2	TOF, DORV	NS
CELL SIGNALING AND ADHESION PROTEINS		
ACVR1/ALK2	AVSD	NS
CRELD1	ASD, AVSD	NS
GJA1	HLHS, VSD, PA	S (oculodentodigital dysplasia) and NS
JAG1	TOF, PVS, PAS	S (Alagille syndrome) and NS
NOTCH1	BAV, AS, HLHS, TOF, PVS	S (Adams-Oliver syndrome) and NS
PDGFRA	TAPVR	NS
SMAD6	BAV, CoA, AS	NS
TAB2	BAV, AS, TOF	NS
STRUCTURAL PROTEINS		
ACTC1	ASD, HCM, DCM, LVNC	NS
DCHS1	MVP	NS
ELN	SVAS	S (Williams-Beuren syndrome) and NS
MYH6	ASD, HCM, DCM	NS
MYH7	Ebstein anomaly, LVNC, HCM, DCM	NS
MYH11	PDA, TAA	NS

AS, Aortic valve stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; DCM, dilated cardiomyopathy; DORV, double-outlet right ventricle; HCM, hypertrophic cardiomyopathy; HLHS, hypoplastic left heart syndrome; LVNC, left ventricular noncompaction cardiomyopathy; MS, mitral valve stenosis; MVP, mitral valve prolapse; NS, nonsyndromic; PA, pulmonary atresia; PAS, pulmonary artery stenosis; PDA, patent ductus arteriosus; PTA, persistent truncus arteriosus; PVS, pulmonary vein stenosis; S, syndromic; SVAS, supravalvar aortic stenosis; TAA, thoracic aortic aneurysm; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 8.

Table 473.5 Clinical Genetic Tests

	GENOMIC VS TARGETED	ANEUPLOIDIES AND CHROMOSOMAL REARRANGEMENTS	COPY NUMBER VARIATION	SNPs AND INDELs	EXAMPLE OF CLINICAL USE
Karyotype	Genomic	+++	+	–	Confirmation of trisomy 21
Array CGH	Genomic	++	+++	–	Multiple congenital anomalies without obvious syndromic association
FISH	Targeted	+	+	–	Suspected 22q11.2 deletion syndrome
Gene panel testing	Targeted	–	+	+++	Suspected monogenic disease with a small differential diagnosis
Exome sequencing	Genomic	–	–	+++	Broad genetic differential diagnosis without obvious syndromic association, or previous negative panel testing
Genome sequencing	Genomic	+	+	+++	Broad genetic differential diagnosis without obvious syndromic association, or previous negative panel testing and need for rapid turnaround time

Sensitivity of tests for the types of genetic variation are indicated as not detected (–), low (+), medium (++), or high (+++). Array CGH indicates comparative genomic hybridization using arrays; FISH, fluorescence in situ hybridization; INDEL, insertion or deletion; and SNP, single nucleotide polymorphism.
From Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation.* 2018;138(21):e653–e711, Table 1.

critical region. At least 30 genes have been mapped to the deleted region; *Tbx1,* a transcription factor involved in early outflow tract development, is one gene that has been implicated as a possible cause of DiGeorge syndrome. The estimated prevalence of 22q11.2 deletions is 1 in 4,000 live births; these occur in 2% of all patients with CHD. Cardiac lesions associated with 22q11.2 deletions are most often seen in association with either DiGeorge syndrome or **Shprintzen (velocardiofacial) syndrome**. The acronym **CATCH 22** has been used to summarize the major components of these syndromes: **C**ardiac defects, **A**bnormal facies, **T**hymic aplasia, **C**left palate, and **H**ypocalcemia. The specific cardiac anomalies are **conotruncal** defects (tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, subarterial VSD) and **branchial arch** defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway anomalies such as tracheomalacia and bronchomalacia are sometimes present. In addition to extracardiac defects, studies in adults with repaired tetralogy of Fallot have linked the presence of a 22q11.2 microdeletion to increased all-cause mortality. Although the risk of recurrence is extremely low in the absence of a parental 22q11.2 deletion, the risk rises to 50% if one parent carries the deletion. More than 90% of patients with the clinical features of DiGeorge syndrome have a deletion at 22q11.2. A second genetic locus on the short arm of chromosome 10 (10p13p14) has also been identified, the deletion of which shares some, but not all, phenotypic characteristics with the 22q11.2 deletion; patients with del(10p) have an increased incidence of sensorineural hearing loss.

Other structural heart lesions associated with specific chromosomal abnormalities include **familial secundum atrial septal defect** (ASD) associated with **heart block** (the transcription factor Nkx2.5 on chromosome 5q35), familial ASD without heart block (the transcription factor GATA4), **Alagille syndrome** (Jagged1 on chromosome 20p12), and **Williams syndrome** (elastin on chromosome 7q11). Of interest, patients with VSDs and atrioventricular septal defects have been found to have multiple Nkx2.5 pathogenic variants in cells isolated from diseased heart tissues, but not from normal heart tissues or from circulating lymphocytes, indicating a potential role for *somatic* rather than germline changes leading to mosaicism in the pathogenesis of congenital heart defects. Tables 473.2 to 473.4 are a compilation of known genetic causes of CHD.

The most progress in identifying the genetic origin of cardiovascular disease has been made in the genetic **cardiomyopathies**, and in particular, **hypertrophic cardiomyopathy** (HCM). Over 1,000 different pathogenic variants in over a dozen genes have been implicated, most of which encode proteins of the cardiac sarcomere, either the contractile thick filament (myosin) or associated regulatory subunits (e.g., troponin or myosin binding protein C), although variants in metabolic/mitochondrial genes are also common in those presenting with HCM in infancy and early childhood. Variants of the cardiac β-**myosin heavy-chain gene *MYH7*** and the **myosin-binding protein C** gene are the most common (Table 473.6), with additional common variants including cardiac troponin T and I, α-tropomyosin, regulatory and essential myosin light chains, titin, and α-myosin heavy chain. Some patients (~15%) may carry variants in more than one sarcomeric gene. Routine clinical laboratory tests are available for most of these genes, so that patients with clinical findings of HCM or children of parents who have been diagnosed with HCM should be tested. However, not all genes causing HCM have been identified, so a negative test does not eliminate a genetic cause.

Progress has also been made in identifying the genetic basis of **dilated cardiomyopathy**, which is familial in 20–30% of cases. Autosomal dominant inheritance is most often encountered, and similar to HCM, multiple genes have been identified (see Table 473.3). X-linked inheritance accounts for 5–10% of cases of familial dilated cardiomyopathy. Pathogenic variants in the dystrophin gene are the most common in this group, causing **Duchenne or Becker muscular dystrophy**. Variants in the gene encoding tafazzin are associated with **Barth syndrome** and for some cases of isolated noncompaction of the left ventricle (LVNC). Autosomal recessive inheritance is associated with a variant in cardiac troponin I. Mitochondrial myopathies may be caused by alterations of enzymes of the electron transport chain encoded by nuclear DNA or enzymes of fatty acid oxidation encoded by mitochondrial DNA. Table 473.6 is a compilation of the most common genetic causes of cardiomyopathy.

The genetic basis of **heritable arrhythmias**, most notably the **long QT syndromes**, has been linked to pathogenic variants of genes coding for subunits of cardiac potassium and sodium channels (Table 473.7). Other heritable arrhythmias include **arrhythmogenic right ventricular dysplasia**, familial atrial fibrillation, familial complete heart block, and **Brugada syndrome**. Table 473.7 is a compilation of the most common genetic causes of arrhythmias.

Of all cases of CHD, 2–4% are associated with known environmental or adverse maternal conditions and teratogenic influences, including

Table 473.6 Genetics of Hypertrophic Cardiomyopathies

CARDIOMYOPATHY	CHROMOSOMAL LOCATION	GENE
Hypertrophic cardiomyopathy	14q1	β-Myosin heavy chain
	15q2	α-Tropomyosin
	1q31	Troponin T
	19p13.2-19q13.2	Troponin I
	11p13-q13	Myosin-binding protein C
	12q23	Cardiac slow myosin regulatory light chain
	13p21	Ventricular slow myosin essential light chain
	2q31	Titin
	3p25	Caveolin-3
	Mitochondrial DNA	tRNA-glycine
	Mitochondrial DNA	tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
OTHER GENETIC DISEASES CAUSING CARDIAC HYPERTROPHY		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25, 12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homolog 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α-Galactoside A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α-glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21	Dystrophin
	Xp28	Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant: Genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ-sarcoglycan; β-myosin heavy chain; cardiac troponin C and T; α-tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α-actinin-2; phospholamban; Cypher/LIM binding domain 3; α-myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.

Isolated noncompaction of the left ventricle: Autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include those for α-dystrobrevin, Cypher/ZASP, lamin A/C, tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management. *Circ Cardiovasc Genet.* 2013;6:118–131.

maternal diabetes mellitus, maternal phenylketonuria, or systemic lupus erythematosus; congenital rubella syndrome; and maternal ingestion of drugs (lithium, ethanol, warfarin, thalidomide, antimetabolites, vitamin A derivatives, anticonvulsant agents). Associated noncardiac malformations noted in identifiable syndromes may be seen in as many as 25% of patients with CHD.

Gender differences in the occurrence of specific cardiac lesions have been identified. Transposition of the great arteries and left-sided obstructive lesions are slightly more common in males (65%), whereas ASD, VSD, PDA, and pulmonic stenosis are more common in females. No ethnic differences in the occurrence of congenital heart lesions as a whole have been noted, although there are some exceptions: supracristal VSD in children of Asian background and transposition of the great arteries, which has a higher occurrence in White infants.

GENETIC COUNSELING

Parents who have a child with CHD require counseling regarding the probability of a cardiac malformation occurring in subsequent children (Table 473.8 and see Chapter 98.1). Except for syndromes caused by a pathogenic variant of a single gene, many forms of CHD, but not all, are still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. When more genetic etiologies are identified, these risks are constantly updated; therefore consultation with a cardiac geneticist or genetic counselor is important.

The degree of severity may vary, as may the presence of associated defects. Careful echocardiographic screening of first-degree relatives will often uncover mild forms of CHD that were clinically silent. For example, the incidence of bicuspid aortic valve is more than double (5% vs 2% in the general population) in the relatives of children with left ventricular outflow obstruction (aortic stenosis, coarctation of the aorta, HLHS). Consultation with a knowledgeable genetic counselor is the most reliable way of providing the family with up-to-date information regarding the risk of recurrence.

Fetal echocardiography improves the rate of detection of congenital heart lesions in at-risk patients (see Chapter 472.4). This type of ultrasound is much more comprehensive than the screening ultrasound performed by an obstetrician and is usually performed and interpreted by a pediatric cardiologist specializing in fetal echocardiography. The resolution and accuracy of fetal echocardiography are excellent but are not perfect; families should be counseled that a normal fetal echocardiogram does not guarantee the absence of CHD. Congenital heart lesions may evolve in the course of the pregnancy; moderate aortic

Table 473.7 Genetics of Arrhythmias

ARRHYTHMIA	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED
Complete heart block	19q13	Not known
Long QT syndrome		
LQT1 (autosomal dominant)	11p15.5	*KVLQT1* (K^+ channel)
LQT2 (autosomal dominant)	7q35	*HERG* (K^+ channel)
LQT3 (autosomal dominant)	3p21	*SCN5A* (Na^+ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	*KCNE1* (K^+ channel)
LQT6	21q22.1	*KCNE2* (K^+ channel)
LQT7	17q23	KCNJ2 (K^+ channel)
LQT8	12p13.3	CACNAIC (L type Ca^{2+} channel)
LQT9	3p25	CAV-3 (caveolin-3, Na^+ current)
LQT10	11q23	SCN4B (Na^+ channel)
LQT11	7q21	AKAP9 (A-kinase anchoring protein)
LQT12	20q11.21	SNTA1 (A1-synthrophin)
LQT13	11q24.3	KCNJ5 (K^+ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5 21q22.1	*KVLQT1* (K^+ channel), KCNE1 (K^+ channel)
Arrhythmogenic right ventricular dysplasia (ARVD): 11 genes are now associated with ARVD (*ARVD1* through *ARVD11*) usually with autosomal dominant inheritance, but with variable penetrance. These genes include *TGFβ_3* (transforming growth factor β), *RYR2* (ryanodine receptor), *LAMR1* (laminin receptor-1), *PTPLA* (protein tyrosine phosphatase), *DSP* (desmoplakin), *PKP2* (plakophilin-2), *DSG2* (desmoglein), and *DSC2* (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16	Not known
	11p15.5	*KVLQT1* (K^+ channel)
	11p15.5	*KCNQ1* (K^+ channel)
	21q22	*KCNE2* (K^+ channel)
	17q23.1-q24.2	*KCNJ2* (K^+ channel)
	7q35-q36	*KCNH2* (K^+ channel)
Brugada syndrome (right bundle branch block, ST segment elevation, unexpected sudden death)	3p21-p24	*SCN5A* (Na^+ channel), rarely CACNA1C, HCN4, TRPM4
	3p22-p24	*GPD1L* (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	1q43	*RYR2* (autosomal dominant)
	1p13.1	*CASQ2* (autosomal recessive)

stenosis with a normal-sized left ventricle at 18 weeks of gestation may progress to aortic atresia with a hypoplastic left ventricle by 34 weeks because of decreased flow through the atria, ventricle, and aorta in the latter half of gestation. This progression has prompted initial clinical trials of interventional treatment, such as fetal aortic balloon valvuloplasty, for the prevention of HLHS (see Chapter 472.7). In addition to diagnosing CHD in utero and subsequent parental counseling, the benefit of fetal ultrasound is that it allows for careful planning of perinatal care, especially in cases where immediate intervention in the neonatal period is warranted.

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Table 473.8 Recurrence Risks for Isolated (Nonsyndromic) Congenital Heart Disease

DEFECT	FATHER AFFECTED (%)	MOTHER AFFECTED (%)	ONE SIBLING AFFECTED (%)	TWO SIBLINGS AFFECTED (%)
ASD	1.5–3.5	4–6	2.5–3	8
AVSD	1–4.5	11.5–14	3–4	10
VSD	2–3.5	6–10	3	10
AS	3–4	8–18	2	6
PVS	2–3.5	4–6.5	2	6
TOF	1.5	2–2.5	2.5–3	8
CoA	2–3	4–6.5	2	6
PDA	2–2.5	3.5–4	3	10
HLHS	21†		2–9*	6
TGA	2†		1.5	5
L-TGA	3–5†		5–6	NR
EA	NR	6	1	3
TrA	NR	NR	1	3
TA	NR	NR	1	3
PA	NR	NR	1	3

*Eight percent recurrence risk for HLHS; up to 22% recurrence risk for any congenital HD.
†Recurrence when one parent is affected, irrespective of sex; used in the absence of sex-stratified risks.
AS, Aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; EA, Ebstein anomaly; HLHS, hypoplastic left heart syndrome; L-TGA, congenitally corrected transposition of the great arteries; NR, not reported/insufficient data; PA, pulmonary atresia; PDA, patent ductus arteriosus; PVS, pulmonary valve stenosis; TA, tricuspid atresia; TGA, D-transposition of the great arteries; TOF, tetralogy of Fallot; TrA, truncus arteriosus; VSD, ventricular septal defect.
From Cowan JR, Ware SM. Genetics and genetic testing in congenital heart disease. *Clin Perinatol*. 2015;42(2): 373–393, Table 5.

Chapter 474

Evaluation and Screening of the Infant or Child with Congenital Heart Disease

Daniel Bernstein

The initial evaluation for suspected congenital heart disease (CHD) involves a systematic approach with two major components (Fig. 474.1). First, congenital cardiac defects can be divided into two major groups based on the presence or absence of **cyanosis**, which can be determined by physical examination aided by pulse oximetry. Second, these groups can usually be further subdivided based on whether the chest radiograph shows evidence of increased, normal, or decreased pulmonary vascular markings. Next, the electrocardiogram (ECG) can be used to determine whether right, left, or biventricular **hypertrophy** exists. The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis. The final diagnosis is then confirmed by echocardiography, cardiac computed tomography (CT) or magnetic resonance imaging (MRI), and/or cardiac catheterization. In a cyanotic or otherwise sick newborn, echocardiographic exam, if available, should not be delayed while awaiting these other modalities.

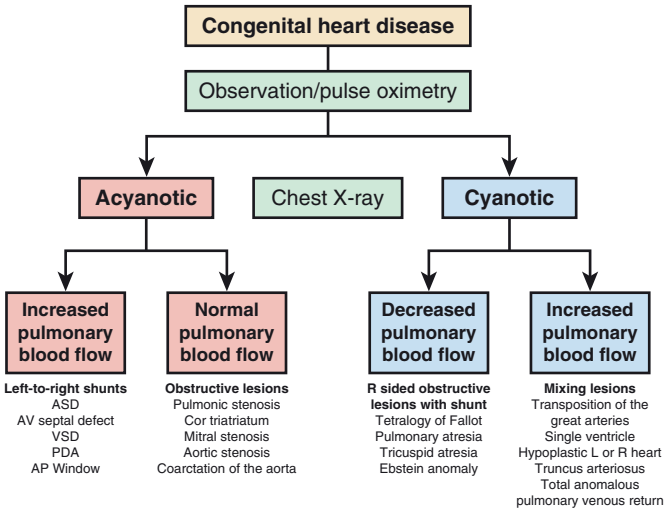

Fig. 474.1 A general algorithmic approach to the initial diagnosis of congenital heart disease, based on observation/pulse oximetry and chest x-ray, to separate patients into four major physiologic subgroups of congenital heart disease. This schematic is a broad, but useful, diagnostic overview; only the most common forms of congenital heart disease are included. A patient's initial presentation may sometimes straddle two of these physiologic groups and can evolve between them over the first week or two of life. For example, in a patient with a VSD, the pulmonary blood flow will be relatively normal in the newborn period and only increase as the pulmonary vascular resistance begins to drop. Similarly, a patient with a mixing lesion may not show pulmonary overcirculation at birth. ASD, Atrial septal defect; AV, atrioventricular; VSD, ventricular septal defect; PDA, patent ductus arteriosus, AP, aortopulmonary; L, left; R, right

Routine **pulse oximetry screening** is recommended for all newborns to detect unsuspected critical cyanotic CHD; lesions include hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, truncus arteriosus, neonatal coarctation of the aorta, and aortic arch hypoplasia/atresia. Many of these lesions are ductal dependent, and if the ductus arteriosus closes, severe cardiac decompensation will ensue. In addition, pulse oximetry may detect respiratory disorders and primary pulmonary hypertension. Screening is performed between 24 and 48 hours of life and before discharge in asymptomatic newborns. The neonate passes if the oxygen saturation is 95% or greater in the right hand or either foot AND the difference is 3% or less between the right hand and foot. The screen is failed if the saturation is less than 90% in either the right hand or foot. If it is between 90% and 94% OR there is more than a 3% difference between the right arm and foot, the screen should be repeated once in 1 hour. If the saturation is 90–94% OR there is a 3% difference after the third screen, urgent **echocardiography** is indicated. In addition, a careful reexamination of the pulses and blood pressure in the upper and lower extremity and cardiac auscultation are indicated in children with an initial positive screen.

ACYANOTIC CONGENITAL HEART LESIONS

Acyanotic congenital heart lesions can be classified according to the predominant physiologic load that they place on the heart. Although many congenital heart lesions induce more than one physiologic disturbance, it is helpful to focus on the primary load abnormality for purposes of classification. The most common lesions are those that produce a **volume load**, and the most common of these are the left-to-right shunt lesions. Atrioventricular (AV) valve regurgitation and dilated cardiomyopathies are other causes of increased volume load. The second major class of lesions causes an increase in **pressure load**, most often secondary to ventricular outflow obstruction (pulmonic or aortic valve stenosis) or narrowing of a great vessel (branch pulmonary artery stenosis or coarctation of the aorta). The chest radiograph and ECG are useful tools for differentiating between these major classes of volume- and pressure-overload lesions while awaiting confirmation with echocardiography.

Lesions Resulting in Increased Volume Load

The most common lesions resulting in increased volume load are those that cause **left-to-right shunting** (see Chapter 475): atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defects (previously known as *AV canal* or *endocardial cushion defects*), and patent ductus arteriosus. The pathophysiologic common denominator in this group is the presence of a **communication** between the systemic and pulmonary sides of the circulation, which results in **shunting** of fully oxygenated blood back into the lungs for a second passage. This shunt can be quantitated by calculating the ratio of pulmonary-to-systemic blood flow (Qp:Qs). Thus a 3:1 shunt implies three times the normal pulmonary blood flow, which is a moderately large shunt likely to cause symptoms of heart failure.

The direction and magnitude of the shunt across such a communication depend on the size of the defect, the relative pulmonary and systemic pressures and vascular resistances, and the compliances of the two chambers connected by the defect. These factors are dynamic and may change dramatically with age; intracardiac defects may grow smaller with time; pulmonary vascular resistance (PVR), which is high in the immediate newborn period, decreases to normal adult levels by several weeks of life; and chronic exposure of the pulmonary circulation to high pressure and blood flow results in a gradual increase in PVR (**Eisenmenger physiology**; see Chapter 482.2). Thus a lesion such as a large VSD may be associated with little shunting and few symptoms during the initial first 2 weeks of life. When PVR declines over the next 2-4 weeks, the volume of the left-to-right shunt increases, and symptoms begin to appear.

The increased volume of blood in the lungs decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitial space and alveoli and causes pulmonary edema. The infant develops the symptoms we refer to as **heart failure**, such as tachypnea, tachycardia, sweating, chest retractions, nasal flaring, and wheezing. For children with large left-to-right shunts, however, the term *heart failure* is a misnomer; total left ventricular output is not decreased but is several times greater than normal, although much of this output is ineffective because it returns through the defect back to the lungs. To maintain this high level of left ventricular output, heart rate and stroke volume are increased, in part mediated by the Frank-Starling relation as the increased ventricular volume stretches the cardiac sarcomeres and in part mediated by an increase in sympathetic nervous system activity. The increase in catecholamine release, combined with the increased work of breathing, results in an elevation in total body oxygen consumption (caused by increased β-receptor stimulation), often beyond the oxygen transport ability of the circulation. Sympathetic activation leads to peripheral vasoconstriction (caused by increased α-receptor stimulation) and to the additional symptoms of sweating and irritability, and the imbalance between oxygen supply and demand leads to failure to thrive. Remodeling of the heart occurs, with predominantly chamber dilation caused by the increased volume load and a lesser degree of hypertrophy. If left untreated, the PVR eventually begins to rise, and by several years of age, the shunt volume will decrease and symptoms will appear to improve. If still uncorrected, the shunt will eventually reverse to right-to-left as the PVR rises (see Chapter 482.2). At this point, the patient may be inoperative if the pulmonary vascular resistance is elevated and fixed (unresponsive to vasodilators), and heart-lung transplant may be the only surgical option.

Additional lesions that impose a volume load on the heart include the **regurgitant lesions** (see Chapter 477) and the **dilated cardiomyopathies** (see Chapter 488.1). Regurgitation through the AV valves is most frequently encountered in patients with partial or complete AV septal defects (AV canal or endocardial cushion defects). In these lesions, the combination of a left-to-right shunt with AV valve regurgitation increases the volume load on the heart and often leads to earlier and more severe symptoms than for isolated septal defects. Regurgitation through the tricuspid valve is seen in **Ebstein anomaly** (see Chapter 479.7). Regurgitation involving one of the semilunar (aortic or pulmonary) valves also results in a volume load but is often also associated with some degree of stenosis, leading to a combined pressure and volume load. Aortic regurgitation may be encountered in patients with a VSD directly under the aortic valve **(supracristal VSD)**, leading to two sources of volume load on the left ventricle.

In contrast to left-to-right shunts, in which intrinsic cardiac muscle contractile function is generally either normal or increased, heart muscle function can be decreased in the cardiomyopathies. **Cardiomyopathies** may affect systolic contractility (dilated cardiomyopathy) or diastolic relaxation (restrictive cardiomyopathy) or both. Decreased cardiac function results in increased atrial and ventricular filling pressure, and pulmonary edema occurs secondary to increased capillary pressure. Poor cardiac output leads to decreased end-organ blood flow, sympathetic activation, and the symptoms of poor perfusion and decreased urine output. The major causes of cardiomyopathy in infants and children include viral myocarditis,

metabolic disorders, and pathogenic gene variants in sarcomeric and other cardiac structural, functional, and energy production genes (see Chapter 488).

Lesions Resulting in Increased Pressure Load

The pathophysiologic common denominator of lesions resulting in increased pressure load is an obstruction to normal blood flow. The most frequent are **obstructions to ventricular outflow**: valvular pulmonic stenosis, valvular aortic stenosis, and coarctation of the aorta (see Chapter 476). Less common are **obstructions to ventricular inflow**: tricuspid or mitral stenosis, cor triatriatum, and obstruction of the pulmonary veins. Ventricular outflow obstruction can occur at the valve, below the valve (double-chambered right ventricle, subaortic membrane), or above the valve (branch pulmonary stenosis or supravalvular aortic stenosis). Unless the obstruction is severe, cardiac output will be maintained and the clinical symptoms of heart failure will be either subtle or absent. The heart compensates for the increased afterload by increasing wall thickness (hypertrophy), but in later stages the affected chamber develops fibrosis and will begin to dilate and can progress to ventricular failure.

The clinical picture is different when obstruction to outflow is severe, which is usually encountered in the immediate newborn period. The infant may become critically ill within several hours of birth. Severe pulmonic stenosis in the newborn period **(critical pulmonic stenosis)** results in signs of right-sided heart failure (hepatomegaly, peripheral edema) and cyanosis from right-to-left shunting across the foramen ovale. Severe aortic stenosis in the newborn period **(critical aortic stenosis)** is characterized by signs of left-sided heart failure (pulmonary edema, poor perfusion), often combined with signs of right-sided failure (hepatomegaly, peripheral edema), and may progress rapidly to total circulatory collapse. In older children, severe untreated pulmonic stenosis leads to symptoms of right-sided heart failure, but usually not to cyanosis unless a pathway persists for right-to-left shunting (e.g., patency of the foramen ovale).

Coarctation of the aorta in older children and adolescents is usually manifested as upper body hypertension and diminished pulses in the lower extremities. In the immediate newborn period, presentation of coarctation can range from decreased pulses in the lower extremities to total circulatory collapse, depending on the severity of the narrowing. The clinical presentation of coarctation may be delayed because of the normally patent ductus arteriosus in the first few days of life. In these patients, even as the ductus begins to close, the open aortic end of the ductus serves as a conduit for blood flow to partially bypass the obstruction; in more severe coarctations, blood leaving the right ventricle traverses the ductus to directly supply the descending aorta (as it did in the fetus). These infants then become symptomatic, often dramatically, when the ductus finally closes, usually within the first few weeks of life. Differential cyanosis (normal saturation in the right arm and low saturation in the foot) is a hallmark sign of this condition, and if picked up on oximetry screen before hospital discharge can be lifesaving.

CYANOTIC CONGENITAL HEART LESIONS

The cyanotic group of congenital heart lesions can also be further divided according to pathophysiology. In one major subdivision, pulmonary blood flow is *decreased,* usually from an **obstruction to right ventricular outflow** (tetralogy of Fallot, tetralogy with pulmonary atresia, or pulmonary atresia with an intact septum) or to an **obstruction to right ventricular inflow** (tricuspid atresia). In the second major subdivision, pulmonary blood flow is *increased* and oxygenated and deoxygenated blood are *mixing* (transposition of the great arteries, single ventricle, truncus arteriosus, total anomalous pulmonary venous return [TAPVR] without obstruction). In the case of TAPVR with obstruction, pulmonary flow is decreased but because there is no exit from the pulmonary veins, the lungs appear to be markedly congested. The chest radiograph is a valuable tool for initial differentiation between these two categories.

Cyanotic Lesions with Decreased Pulmonary Blood Flow

For cyanosis to occur, these lesions must include both an obstruction to pulmonary blood flow (at the tricuspid valve or pulmonary valve level) *and* a pathway by which systemic venous blood can shunt from right to left and enter the systemic circulation (via a patent foramen ovale, ASD, or VSD). Common lesions in this group include tricuspid atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, pulmonary atresia with intact septum (with atrial-level shunting), and various forms of single ventricle with pulmonary stenosis or atresia (see Chapter 457). In these lesions, the degree of cyanosis depends on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may be absent at rest. However, these patients may have hypercyanotic (tet) spells during conditions of stress. In contrast, if the obstruction is severe, pulmonary blood flow may be totally dependent on patency of the ductus arteriosus. When the ductus closes in the first few days of life, the neonate experiences profound hypoxemia.

Cyanotic Lesions with Increased Pulmonary Blood Flow

This group of lesions is not associated with obstruction to pulmonary blood flow. Cyanosis is caused by either abnormal ventricular-arterial connections or total mixing of systemic venous (deoxygenated) and pulmonary venous (oxygenated) blood within the heart (see Chapter 480). **Transposition of the great arteries** (or **vessels**) is the most common of the former group of lesions. In this condition the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. Systemic venous blood returning to the right atrium is pumped directly back to the body, and oxygenated blood returning from the lungs to the left atrium is pumped back into the lungs. The **persistence of fetal pathways** (foramen ovale and ductus arteriosus) allows for some degree of mixing in the immediate newborn period, keeping the systemic saturation from falling until the ductus begins to close; these infants can then become extremely cyanotic quite precipitously.

Total mixing lesions include cardiac defects with a common atrium or ventricle, TAPVR, and truncus arteriosus (see Chapter 480). In this group, deoxygenated systemic venous blood and oxygenated pulmonary venous blood mix completely at some location in the heart, and as a result, the oxygen saturation is equal in the pulmonary artery and aorta. If pulmonary blood flow is not obstructed, these infants have a combination of cyanosis and pulmonary overcirculation leading to heart failure. In contrast, if pulmonary stenosis is present, these infants may have cyanosis alone, similar to patients with tetralogy of Fallot.

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Chapter 475

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions

475.1 Atrial Septal Defect

Daniel Bernstein

Atrial septal defects **(ASDs)** can occur in any portion of the atrial septum—**secundum**, **primum**, or **sinus venosus**—depending on which embryonic septal structure has failed to develop normally (Fig. 475.1) (see Chapter 469). Less often, the atrial septum may be almost absent, with the creation of a functional single atrium. Isolated secundum ASDs account for approximately 7% of all congenital heart defects. The majority of cases of ASD are sporadic; autosomal dominant inheritance does occur as part of **Holt-Oram syndrome** (hypoplastic or absent thumbs, radii, triphalangism, phocomelia, first-degree heart block, ASD) or in families with both secundum ASD and heart block (see Table 473.2).

An isolated valve-incompetent **patent foramen ovale (PFO)** is a common echocardiographic finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased right atrial pressure (pulmonary stenosis or atresia, tricuspid valve abnormalities, right ventricular dysfunction), venous blood may shunt across the PFO into the left atrium with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive left atrium (e.g., secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-patent (able to be pushed opened with a catheter) PFO may be present in 15–30% of adults. An isolated PFO does not require surgical treatment, although it is a risk for paradoxical (right-to-left) systemic embolization. In adults who have had a thromboembolic stroke, echocardiographic screening for a PFO is routinely performed, and device closure of the PFO is a common treatment option.

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475.2 Ostium Secundum Defect

Daniel Bernstein

An ostium secundum defect in the region of the fossa ovalis is the most common form of ASD and is associated with structurally normal atrioventricular (AV) valves (see Fig. 475.1). **Mitral valve prolapse** has been described in association with this defect but is rarely an important clinical consideration. Secundum ASDs may be single or multiple (fenestrated atrial septum), and openings ≥2 cm in diameter are common in symptomatic older children. Large defects may extend inferiorly toward the inferior vena cava (IVC) and ostium of the coronary sinus, superiorly toward the superior vena cava (SVC), or posteriorly. Females outnumber males 3:1 in incidence. **Partial anomalous pulmonary venous return** (PAPVR), usually of the right upper pulmonary vein, may be an associated lesion.

PATHOPHYSIOLOGY

The degree of left-to-right shunting depends on the size of the defect, the relative compliance of the right and left ventricles, and the relative vascular resistance in the pulmonary and systemic circulations. In large defects, a considerable shunt of oxygenated blood flows from the left to the right atrium (Fig. 475.2). This blood is added to the usual venous return to the right atrium and is pumped by the right ventricle to the lungs. With large defects, the ratio of pulmonary-to-systemic blood flow (Qp:Qs) is usually between 2:1 and 4:1. The paucity of symptoms in infants with ASDs is related to the structure of the right ventricle in early life, when its muscular wall is still thick and less compliant, thus limiting the left-to-right shunt. As the infant becomes older and pulmonary vascular resistance (PVR) drops, the right ventricular (RV) wall becomes thinner, and the left-to-right shunt across the ASD increases. The increased blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilation of the pulmonary artery. The left atrium may also be enlarged as the increased pulmonary blood flow returns to the left atrium, but the left ventricle and aorta are normal in size. Despite the large pulmonary blood flow, pulmonary arterial pressure is usually initially normal

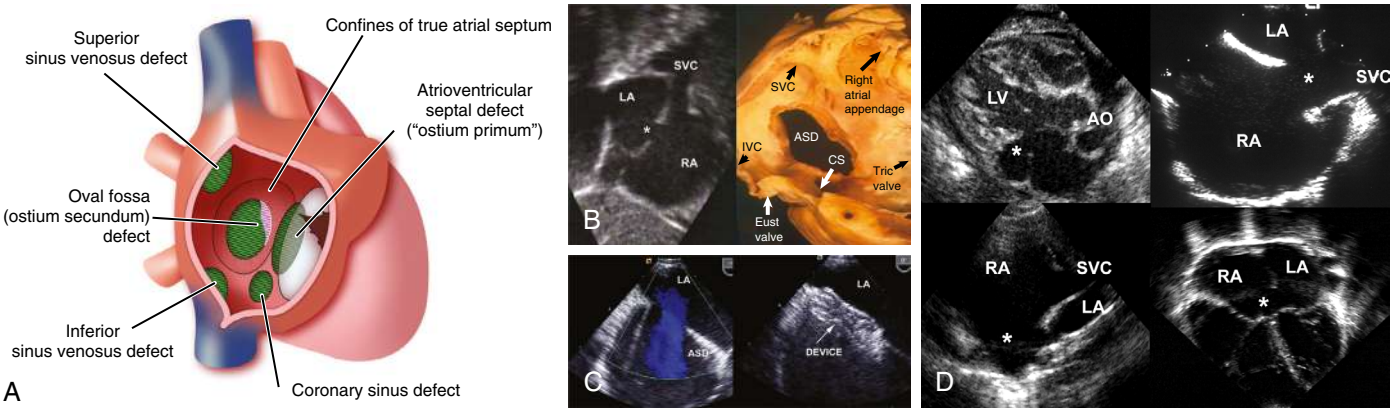

Fig. 475.1 Atrial septal defects (ASDs). **A,** Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. **B,** *Left,* Subcostal right anterior oblique view of a secundum ASD *(asterisk)* that is suitable for device closure. *Right,* Specimen as seen in a similar view, outlining the landmarks of the defect. **C,** *Left,* Transesophageal echocardiogram with color flow before device closure. *Right,* Taken after release of an Amplatzer device. **D,** Montage of echocardiographic interatrial communications that are not secundum ASDs *(asterisks)* and therefore not suitable for device closure. *Top left,* Coronary sinus defect caused by unroofing; *top right,* superior sinus venosus defect; *bottom left,* inferior sinus venosus defect; *bottom right,* ASD in the setting of an atrioventricular septal defect. AO, Aorta; CS, coronary sinus; Eust, eustachian; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; SVC, superior vena cava; Tric, tricuspid. *(From Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig 75.17, p. 1536.)*

because of the absence of a high-pressure communication between the pulmonary and systemic circulations. PVR remains low throughout childhood, although it may begin to increase in adulthood and may eventually result in reversal of the shunt and clinical cyanosis **(Eisenmenger syndrome)**.

CLINICAL MANIFESTATIONS

A child with an ostium secundum ASD is often asymptomatic; the lesion is often discovered during routine physical examination. Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood. However, on closer evaluation, younger children may show subtle signs of failure to thrive, and older children may have varying degrees of exercise intolerance. Often, the degree of limitation may go unnoticed by the family until after repair, when the child's growth or activity level greatly increases.

The physical findings of an ASD are usually characteristic but fairly subtle and require careful examination of the heart, paying special attention to the heart sounds. Examination of the chest may reveal a mild left precordial bulge. An RV systolic lift may be palpable at the left sternal border. Sometimes a pulmonic ejection click can be heard. In most patients with an ASD, the characteristic finding is that the second heart sound (S_2) is **widely split and fixed** in its splitting during all phases of respiration. Normally, the duration of RV ejection varies with respiration, with inspiration increasing RV volume and delaying closure of the pulmonary valve, widening the S_2 split. With an ASD, RV diastolic volume is constantly increased because of the shunt, and ejection time is prolonged throughout all phases of respiration. A systolic ejection murmur is heard; it is usually no greater than a grade 3/6, medium pitched, without harsh qualities, seldom accompanied by a thrill, and best heard at the left middle and upper sternal border. It is produced by the increased flow across the RV outflow tract into the pulmonary artery. Because the atria are at low pressure, flow across the ASD itself does not cause an audible murmur. A short, rumbling mid-diastolic murmur produced by the increased volume of blood flow across the tricuspid valve (see Fig. 475.2) is often audible at the lower-left sternal border. This finding, which may be subtle and is heard best with the bell of the stethoscope, usually indicates a Qp:Qs ratio of at least 2:1.

DIAGNOSIS

The chest radiograph shows varying degrees of enlargement of the right ventricle and atrium, depending on the size of the shunt. The pulmonary artery is enlarged, and pulmonary vascularity is increased. These signs vary and may not be conspicuous in mild cases. Cardiac enlargement is often best appreciated on the lateral chest radiograph because the right ventricle protrudes anteriorly as its volume increases. The **electrocardiogram** (ECG) shows RV volume overload: the QRS axis may be normal or exhibit right axis deviation, and a minor RV conduction delay (rsR′ pattern in the right precordial leads) may be present (Fig. 475.3). **Right ventricular hypertrophy** would be unusual

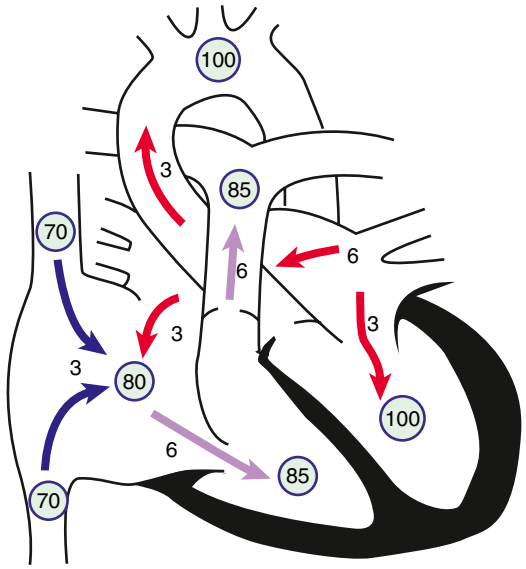

Fig. 475.2 Physiology of atrial septal defect (ASD). *Circled numbers* represent oxygen saturation (S_{O_2}) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in S_{O_2} in the right atrium. Six liters of blood flow through the tricuspid valve and cause a mid-diastolic flow rumble. S_{O_2} may be slightly higher in the right ventricle because of incomplete mixing at the atrial level. The full 6 L flow across the right ventricular outflow tract and cause a systolic ejection flow murmur. Six liters return to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output).

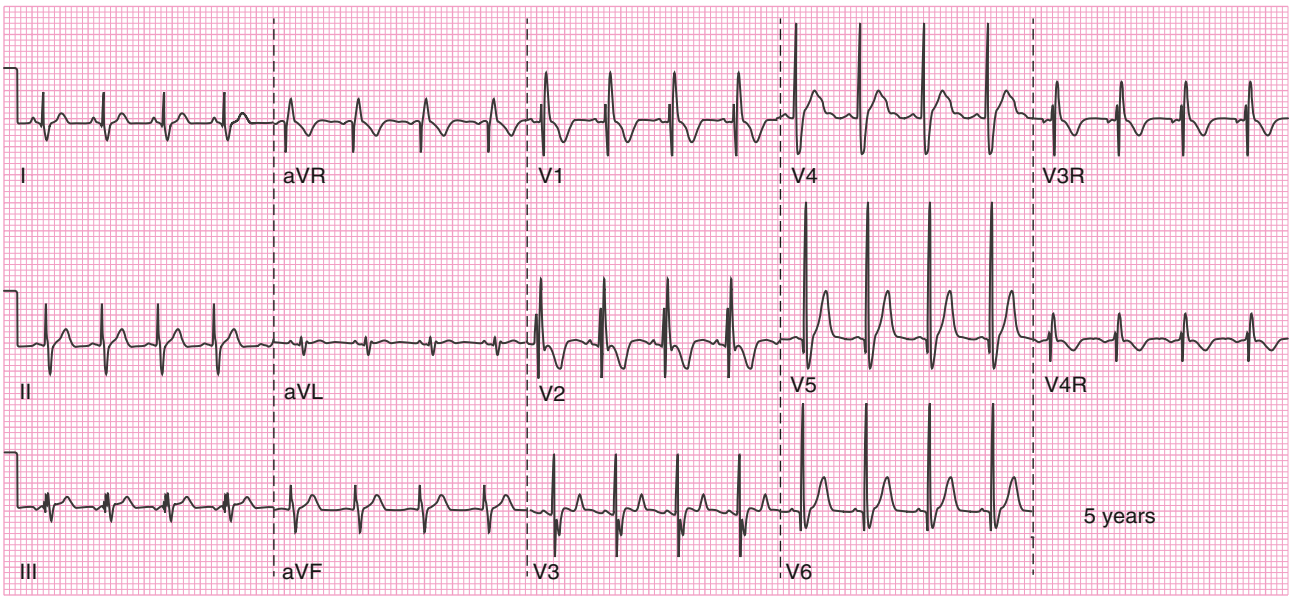

Fig. 475.3 Electrocardiogram in a child with an atrial septal defect showing rSR′ pattern (minor RV conduction delay) pattern in the right precordial leads.

in the absence of pulmonary hypertension or other lesions (e.g., valvar pulmonic stenosis).

The **echocardiogram** shows findings characteristic of RV volume overload, including an increased RV end-diastolic dimension and flattening and abnormal motion of the ventricular septum (see Fig. 475.1). A normal septum moves posteriorly during systole and anteriorly during diastole (synchronous with the left ventricular contractions). With RV overload and normal PVR, septal motion is either flattened or reversed—that is, anterior movement in systole. The location and size of the ASD are readily appreciated by two-dimensional (2D) scanning, with a characteristic brightening of the echo image seen at the edge of the defect caused by the increased reflectivity of ultrasound at the tissue-blood interface (T-artifact). The shunt is confirmed by pulsed and color flow Doppler. The normal entry of all pulmonary veins into the left atrium should be confirmed given the potential for anomalous return of the right upper pulmonary vein.

Patients with the classic features of a hemodynamically significant ASD on physical examination and chest radiography in whom echocardiographic identification of an isolated secundum ASD is made need not undergo diagnostic catheterization before repair, with the exception of an older patient, in whom PVR may be a concern. If pulmonary vascular disease is suspected, cardiac catheterization confirms the presence of the defect and allows measurement of the shunt ratio and pulmonary pressure and resistance.

If catheterization is performed, usually at the time of device closure, the oxygen content of blood from the right atrium will be much higher than that from the SVC (see Fig. 475.2). This feature is not specifically diagnostic because it may occur with PAPVR to the right atrium, with a **ventricular septal defect** (VSD) in the presence of tricuspid insufficiency, with AV septal defects associated with left ventricular–to–right atrial shunts, and with aorta–to–right atrial communications (ruptured sinus of Valsalva aneurysm). Pressure in the right side of the heart is usually normal, but small to moderate pressure gradients (<25 mm Hg) may be measured across the RV outflow tract because of functional pulmonary stenosis related to excessive blood flow. If the pressure gradient across the pulmonary valve is greater, pathologic pulmonary stenosis is likely present. In children and adolescents, PVR is almost always normal. The shunt is variable and depends on the size of the defect, but it may be of considerable volume. **Cineangiography**, performed with the catheter through the defect and in the right upper pulmonary vein, demonstrates the defect and confirms the location of the right upper pulmonary venous drainage (normal or aberrant into the SVC). **Pulmonary angiography** demonstrates the defect on the *levophase* (return of contrast to left side of the heart after passing through the lungs).

COMPLICATIONS

Secundum ASDs are usually isolated, although they may be associated with PAPVR, pulmonary valvular stenosis, VSD, pulmonary artery branch stenosis, and persistent left SVC, as well as mitral valve prolapse and insufficiency. Secundum ASDs are associated with autosomal dominant **Holt-Oram syndrome**. The gene responsible for this syndrome, situated in the region 12q21-q22 of chromosome 12, is *TBX5,* a member of the T-box transcriptional family. A **familial form of secundum ASD** associated *with* AV conduction delay has been linked to pathogenic variants in another transcription factor, Nkx2.5. Patients with **familial ASD** *without* heart block may carry a variant in the transcription factor GATA4, located on chromosome 8p22-23 (see Table 473.2).

TREATMENT

Transcatheter device or surgical closure is advised for all symptomatic patients and for asymptomatic patients with a Qp:Qs ratio of at least 2:1 and those with RV enlargement. The timing for elective closure is usually after the first year of life and before entry into school. Closure carried out at open heart surgery is associated with a mortality rate of <1%. Repair is preferred during early childhood because surgical mortality and morbidity are significantly greater in adulthood; the long-term risk of arrhythmia caused by chronic atrial dilation is also greater after ASD repair in adults. For most patients, *the procedure of choice is percutaneous catheter device closure using an atrial septal occlusion device,* implanted transvenously in the cardiac catheterization laboratory (Fig. 475.4). The results are excellent, and patients are usually discharged from the hospital the following day. The incidence of serious complications (e.g., device erosion) is very low and can be decreased by identifying high-risk patients, such as those with a deficient rim of septum in the area where the device would be anchored. Echocardiography can usually determine whether a patient is a good candidate for device closure. In patients with small secundum ASDs and minimal left-to-right shunts without RV enlargement, the consensus is that closure is usually not required. Infants with small to moderate-sized ASDs can be watched closely, because these defects will often grow smaller in the first year of life. It is unclear whether the persistence of a small ASD into adulthood increases the risk for stroke enough to warrant prophylactic closure of these defects in all patients, including those with no history of stroke.

PROGNOSIS

Small to moderate-sized ASDs detected in term infants may grow smaller or close spontaneously. Secundum ASDs are well tolerated during childhood, and significant symptoms do not usually appear until the third decade or later. Pulmonary hypertension, atrial dysrhythmias, tricuspid or mitral insufficiency, and heart failure are late manifestations; these symptoms may initially appear

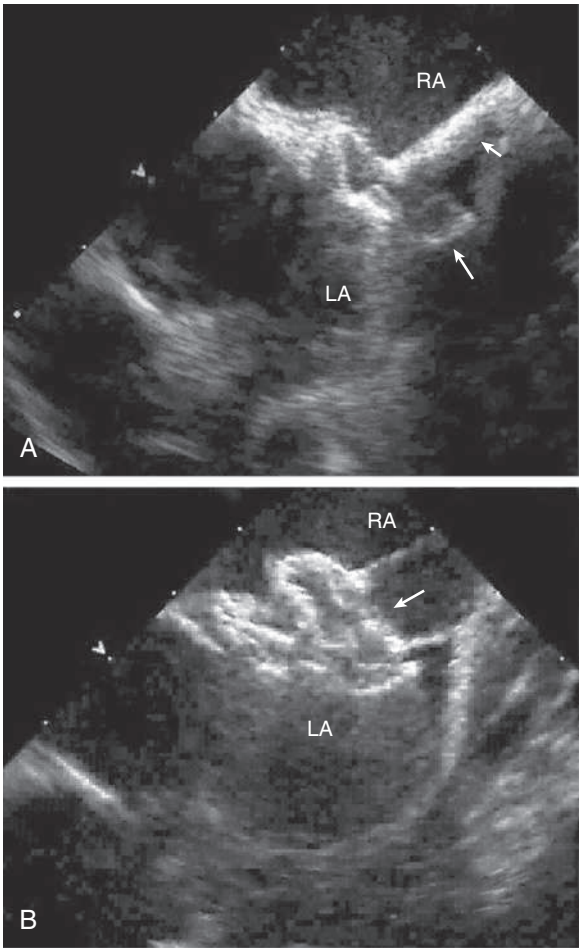

Fig. 475.4 Intravascular ultrasound imaging of transcatheter occlusion of an atrial septal defect (ASD). **A,** Catheter *(small arrow)* has been advanced across the ASD, and the left-sided disk of the device *(large arrow)* has been extruded from the sheath into the left atrium (LA). **B,** The right atrial disk *(arrow)* has now been extruded into the right atrium (RA). The two halves of the device are then locked together and the catheter detached from the occluder device and removed.

during the increased volume load of pregnancy. Infective endocarditis is extremely rare, and antibiotic prophylaxis for isolated secundum ASDs is not recommended.

The results after surgical or device closure in children with moderate-sized to large shunts are excellent. Symptoms, if present, disappear rapidly, and growth is frequently enhanced. Heart size decreases to normal, and the ECG shows decreased RV volume load. Late right-sided heart failure and arrhythmias are less common in patients who have had early repair, becoming more common in patients who undergo surgery after 20 years of age. Although early and midterm results with device closure are excellent, the long-term effects are not yet known. Reports of resolution of migraine headaches with aura in patients after device closure of an ASD or PFO suggest a possible thromboembolic etiology; however, whether to close such defects is still unclear.

475.3 Sinus Venosus Atrial Septal Defect

Daniel Bernstein

A sinus venosus ASD is situated in the upper part of the atrial septum in close relation to the entry of the superior vena cava (see Fig. 475.1). Often, one or more pulmonary veins (usually from the right lung) drain anomalously into the SVC. The SVC sometimes straddles the defect; in this case, some systemic venous blood enters the left atrium, but only rarely does it cause clinically evident cyanosis. The hemodynamic disturbance, clinical picture, ECG, and radiograph are similar to those seen in secundum ASD. The **diagnosis** can usually be made by echocardiography. If questions remain after echocardiogram regarding pulmonary venous drainage, cardiac CT or MRI is usually diagnostic. Cardiac catheterization is rarely required, except in adult patients in whom PVR assessment may be important. **Anatomic correction** generally requires surgical insertion of a patch to close the defect while incorporating the entry of any anomalous pulmonary veins into the left atrium. If the anomalous vein drains high in the SVC, the vein can be left intact and the ASD closed to incorporate the SVC mouth into the left atrium. The SVC proximal to the venous entrance is then detached and anastomosed directly to the right atrial appendage (Warden procedure). This procedure avoids direct suturing of the pulmonary vein, with less chance of future stenosis. Surgical results are generally excellent. Rarely, sinus venosus defects involve the IVC.

475.4 Partial Anomalous Pulmonary Venous Return

Daniel Bernstein

One or several pulmonary veins may return anomalously to the SVC or IVC, right atrium, or coronary sinus and produce a left-to-right shunt of oxygenated blood. *Partial* anomalous pulmonary venous return (PAPVR) usually involves some or all of the veins from only one lung, typically the right. When an associated ASD is present, it is generally of the sinus venosus type but can be secundum (see Chapters 475.2 and 475.3). When an ASD is detected by echocardiography, one must always search for associated PAPVR. The history, physical signs, and electrocardiographic and radiologic findings are indistinguishable from those of an isolated ostium secundum ASD. Occasionally, an anomalous vein draining into the IVC is visible on chest radiography as a crescentic shadow of vascular density along the right border of the cardiac silhouette **(scimitar syndrome)**; in these patients an ASD is not usually present, but **pulmonary sequestration** or **lung hypoplasia** and anomalous arterial supply to that lobe are common findings. **Total anomalous pulmonary venous return** (TAPVR) is a cyanotic lesion and is discussed in Chapter 480.7. Echocardiography generally confirms the diagnosis. MRI and CT are also useful if there is a question regarding pulmonary venous drainage or in cases of scimitar syndrome. If cardiac catheterization is performed, the presence of anomalous pulmonary veins is demonstrated by selective pulmonary arteriography, and anomalous pulmonary arterial supply to the right lung is demonstrated by descending aortography.

The prognosis for PAPVR is excellent, similar to that for ostium secundum ASDs. When a significant left-to-right shunt is present, surgical repair is performed. The associated ASD should be closed in such a way that pulmonary venous return is directed to the left atrium. A single anomalous pulmonary vein without an atrial communication may be difficult to redirect to the left atrium; if the shunt is small and the right ventricle is not enlarged, it may be left unoperated.

475.5 Atrioventricular Septal Defects (Ostium Primum and Atrioventricular Canal or Endocardial Cushion Defects)

Daniel Bernstein

The abnormalities encompassed by atrioventricular (AV) septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a **deficiency of the AV septum**. In the normal heart, the tricuspid valve sits slightly lower (more toward the cardiac apex) than does the mitral valve, and thus a small portion of septum (the AV septum) separates the left ventricle from the right atrium. This septum is deficient in all forms of AV septal defect. When the AV septum is absent and there is also an **ostium primum** defect, the main communication is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most cases a **cleft in the anterior leaflet of the mitral valve** is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is present. The ventricular septum is intact.

An **AV septal defect**, formerly known as an *AV canal defect* or *endocardial cushion defect,* consists of a defect of the AV septum and contiguous atrial and ventricular septal defects with a common AV valve. The severity of the AV valve abnormality varies considerably. In a **complete AV septal defect**, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each ventricle. The anterior bridging leaflet can be divided into right- and left-sided components or may be single and free floating over the ventricular septum. Complete AV septal defect is one of the most common forms of congenital heart disease in children with **Down syndrome**.

Transitional varieties of these defects also occur and include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets and small VSDs and, less commonly, ostium primum defects with normal AV valves. In some patients the atrial septum is intact but a VSD is seen in the inlet septum, similar to that found in the complete form of AV septal defect. Sometimes, AV septal defects are associated with varying degrees of hypoplasia of one of the ventricles, known as either **left-dominant** or **right-dominant AV septal defect**. If the affected ventricular chamber is too small to establish a two-ventricle circulation, surgical palliation, aiming for an eventual Fontan procedure, is performed (see Chapters 479.4 and 480.10).

PATHOPHYSIOLOGY

In ostium primum defects, the basic abnormality is the combination of a left-to-right shunt across the atrial defect and mitral (or occasionally tricuspid) insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary artery pressure (PAP) is typically normal or only mildly increased. The physiology of this lesion is therefore similar to that of an ostium secundum ASD.

In complete AV septal defects, left-to-right shunting occurs at both the atrial and the ventricular level (Fig. 475.5). Additional shunting may occur directly from the left ventricle to the right atrium (known as a *Gerbode shunt*) because of absence of the AV septum. Pulmonary

hypertension and an early tendency to increase PVR are common. AV valvular insufficiency, which may be moderate to severe, further increases the volume load on one or both ventricles. If the defect is large enough, some right-to-left shunting may also occur at the atrial and ventricular levels and lead to mild arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (**Eisenmenger physiology**; see Chapter 482.2). The risk for development of pulmonary vascular disease is greater in patients with Down syndrome, and therefore surgical correction is usually considered early in these patients, within the first 3-6 months of life.

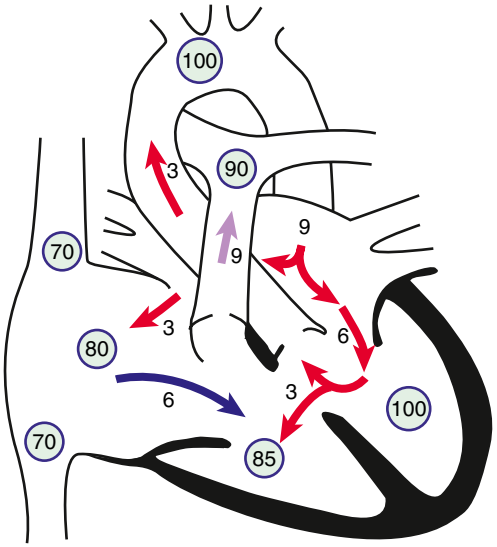

Fig. 475.5 Physiology of atrioventricular (AV) septal defect. *Circled numbers* represent oxygen saturation (S_{O_2}) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 3:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and mixes with 3 L of fully saturated blood shunting left to right across the atrial septal defect; the result is an increase in S_{O_2} in the right atrium. Six liters of blood flow through the right side of the common AV valve, joined by an additional 3 L of saturated blood shunting left to right at the ventricular level, further increasing S_{O_2} in the right ventricle. The full 9 L flow across the right ventricular outflow tract into the lungs. Nine liters return to the left atrium, with 3 L shunting left to right across the defect and 6 L crossing the left side of the common AV valve and causing a mid-diastolic flow rumble. Three liters of this volume shunt left to right across the ventricular septal defect, and 3 L are ejected into the ascending aorta (normal cardiac output).

CLINICAL MANIFESTATIONS

Many children with an isolated ostium primum defect are asymptomatic, and the anomaly is discovered during a general physical examination. In patients with moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical holosystolic murmur caused by mitral insufficiency.

A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. In these patients, cardiac enlargement is moderate or marked and the precordium is hyperdynamic. Auscultatory signs produced by the left-to-right shunt include a normal or accentuated first heart sound (S_1); wide, fixed splitting of S_2; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower-left sternal edge or apex, or both, as a result of increased flow through the AV valves. **Mitral insufficiency** may be manifested by a harsh (occasionally very high-pitched) **apical holosystolic murmur** that radiates to the left axilla.

With *complete* AV septal defects, heart failure and intercurrent pulmonary infection usually appear in infancy. The liver is enlarged, and the infant often develops respiratory symptoms, feeding intolerance, and failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower-left sternal border. A precordial bulge and lift may be present as well. S_1 is normal or accentuated. S_2 is fixed and widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower-left sternal border, indicative of increased blood flow across the right side of the common AV valve, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.

DIAGNOSIS

Chest radiographs of children with complete AV septal defects often show moderate to severe cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The ECG in patients with a complete AV septal defect is *distinctive* and usually diagnostic. Principal abnormalities include (1) superior and rightward orientation of the mean frontal QRS axis (−90 to −180 degrees) represented by the QRS being negative in both lead I and lead aVF, (2) counterclockwise inscription of the superiorly oriented QRS vector loop (manifested by a Q wave in leads I and aVL), (3) signs of biventricular hypertrophy or isolated RV hypertrophy, (4) RV conduction delay (rSR′ pattern in leads V_3R and V_1), (5) normal or tall P waves, and (6) occasional prolongation of the P-R interval (Fig. 475.6).

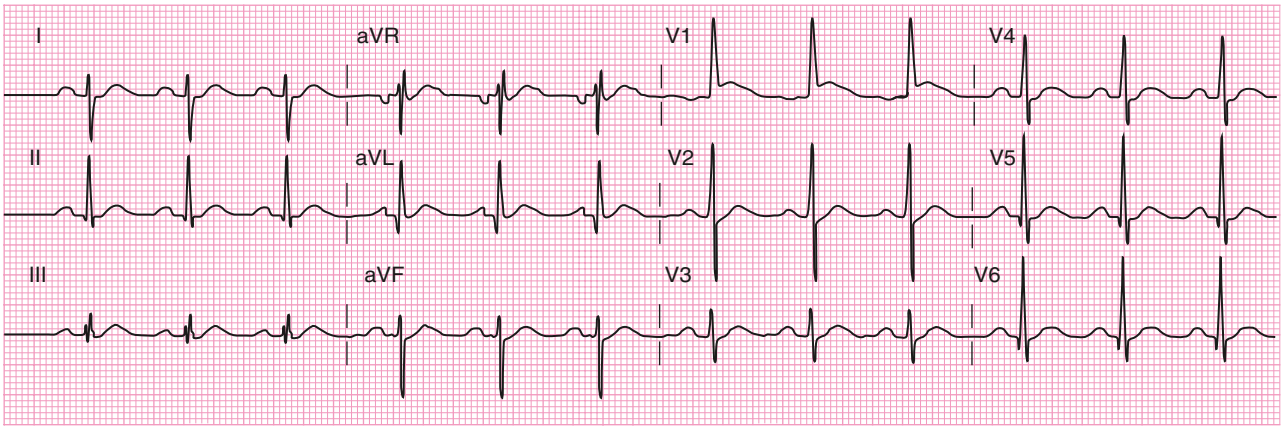

Fig. 475.6 Electrocardiogram from an infant with atrioventricular septal defect. Note that the QRS complexes are negative in both leads I and roughly equipotential in lead III, so the QRS axis is −150 degrees. There is also right ventricular hypertrophy (RVH) and a minor right ventricular conduction delay with an RSR′ pattern in aVR.

The echocardiogram is diagnostic and shows signs of RV enlargement (Fig. 475.7). There is encroachment of the mitral valve into the left ventricular outflow tract (LVOT); the abnormally low position of the AV valves results in a "gooseneck" deformity of the LVOT. In normal hearts the tricuspid valve inserts slightly more toward the apex than does the mitral valve. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects, the inlet portion of the ventricular septum is also deficient, and the common AV valve is readily appreciated. Pulsed and color flow Doppler echocardiography will demonstrate left-to-right shunting at the atrial, ventricular, or left ventricular–to–right atrial levels and can be used to semiquantitate the degree of AV valve insufficiency. Echocardiography is useful for determining the insertion points of the chordae of the common AV valve, the relative size of the two ventricles, and evaluating the presence of associated lesions such as patent ductus arteriosus (PDA) or coarctation of the aorta.

Cardiac catheterization and angiocardiography are rarely required to confirm the diagnosis unless pulmonary vascular disease is suspected, as when the diagnosis has been delayed beyond early infancy, especially in patients with Down syndrome in whom the development of pulmonary vascular disease may be more rapid. Catheterization demonstrates the magnitude of the left-to-right shunt, the degree of PVR elevation, and the severity of insufficiency of the common AV valve. By oximetry, the shunt is usually demonstrable at both the atrial and the ventricular level. Arterial oxygen saturation is normal or only mildly reduced unless pulmonary vascular disease is present. Children with ostium primum defects generally have normal or only moderately elevated PAP. Conversely, complete AV septal defects are associated with RV and pulmonary arterial hypertension and, in older patients, increased PVR (see Chapter 482.2).

Selective left ventriculography will demonstrate deformity of the common AV valve and distortion of the LVOT caused by the abnormally apical position of this valve (gooseneck deformity). The abnormal anterior leaflet of the mitral valve is serrated, and insufficiency is noted. Direct shunting of blood from the left ventricle to the right atrium may also be demonstrated.

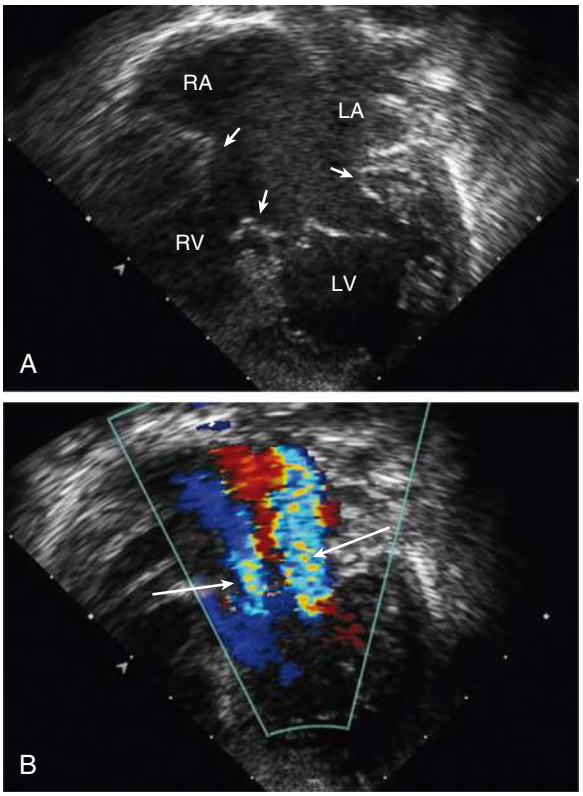

Fig. 475.7 Echocardiograms of atrioventricular (AV) septal defect. **A,** Subcostal four-chamber view demonstrating the common AV valve *(arrows)* spanning the atrial and ventricular septal defects. **B,** Doppler imaging shows two jets of regurgitation through the left side of the common AV valve *(arrows)*. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT

Ostium primum defects are approached surgically from an incision in the right atrium. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of a patch prosthesis. The surgical mortality rate for ostium primum defects is very low.

Surgical treatment of complete AV septal defects is more complex, although highly successful. The postoperative course may be prolonged in infants with severe cardiac failure and in those with pulmonary hypertension. Because of the risk of **pulmonary vascular disease** developing as early as 6-12 months of age, surgical intervention must be performed during infancy. Full correction of these defects can be readily accomplished. Palliation with *pulmonary arterial banding* is uncommon now and reserved for the small subset of patients who have other associated lesions that make early corrective surgery too risky. However, banding may not be effective in patients with a large amount of AV valve regurgitation, as the higher pressure will only increase the regurgitation. The atrial and ventricular defects are patched, using either one or two separate patches, and the AV valves are reconstructed. Uncommon complications include surgically induced heart block requiring placement of a permanent pacemaker and excessive LVOT narrowing requiring surgical revision. More common long-term complications include residual tricuspid or mitral regurgitation, because full repair of very abnormal valves is often not possible. This requires long-term surveillance because these patients may require replacement with a prosthetic valve later in life.

PROGNOSIS

The prognosis for unrepaired complete AV septal defects depends on the magnitude of the left-to-right shunt, degree of PVR elevation, and severity of AV valve insufficiency. Before the advent of early corrective surgery, death from cardiac failure during infancy was common, and patients who survived without surgery usually developed pulmonary vascular disease. Most unoperated patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the third or fourth decade of life, similar to the course of patients with secundum ASDs. Today, long-term results after surgical repair are excellent. Late postoperative **complications** include atrial arrhythmias and heart block, progressive narrowing of the LVOT requiring surgical revision, and eventual worsening of AV valve regurgitation (usually on the left side) requiring reoperation or replacement with a prosthetic valve.

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475.6 Ventricular Septal Defect

Daniel Bernstein

Ventricular septal defect is the most common cardiac malformation and accounts for 25% of cases of congenital heart disease. Defects may occur in any portion of the ventricular septum, but the most common are of the **membranous** type (Fig. 475.8). These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of tetralogy of Fallot (see Chapter 479.1). VSDs superior to the crista supraventricularis **(supracristal)** are less common; these are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency (see Chapter 475.7). Supracristal

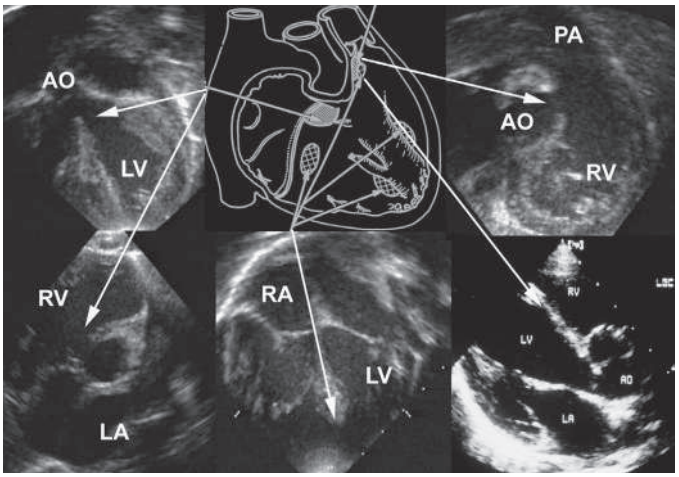

Fig. 475.8 Different types of ventricular septal defects (VSDs). The **central diagram** outlines the location of the various types of defects as seen from the right ventricle. **Two left images** show a perimembranous VSD as seen in the five-chamber and short-axis views. Note the defect is roofed by the aorta and is next to the tricuspid valve. **Bottom middle** echocardiogram shows a muscular apical defect. **Top right image** is a right anterior oblique view in a doubly committed VSD. **Bottom right image** is a short axis view showing an outlet VSD with prolapse of the right coronary cusp. AO, Aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. *(From Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig 75.21, p. 1514.)*

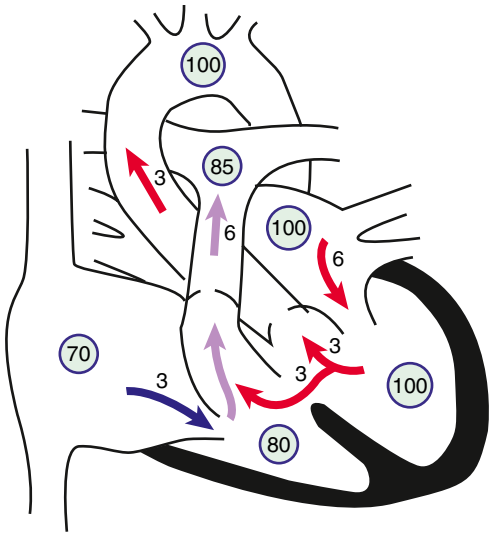

Fig. 475.9 Physiology of a moderate-to-large ventricular septal defect. *Circled numbers* represent oxygen saturation (So_2) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunt left to right across the VSD, resulting in increased So_2 in the right ventricle. Six liters of blood are ejected into the lungs (2:1 shunt). Pulmonary arterial saturation may be further increased because of incomplete mixing at the right ventricular level. Six liters return to the left atrium, cross the mitral valve, and cause a mid-diastolic flow rumble. Three liters of this volume shunt left to right across the VSD, and 3 L are ejected into the ascending aorta (normal cardiac output).

VSDs are more common in patients of Asian descent. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple ("Swiss cheese" septum).

PATHOPHYSIOLOGY

The physical size of the VSD is a major determinant of the size of the left-to-right shunt. When the defect is large, the level of pulmonary vascular resistance (PVR) in relation to systemic vascular resistance (SVR) is the major determinant of the shunt's magnitude, since the large defect will essentially equalize pressure between the two ventricles. When a small communication is present (usually <5 mm), the VSD is deemed to be pressure **restrictive**, meaning that right ventricular (RV) pressure is normal or only slightly elevated. The higher pressure in the left ventricle drives the shunt left to right, and the size of the defect limits the magnitude of the shunt. In larger, **nonrestrictive** VSDs (usually >10 mm), RV and left ventricular (LV) pressures are equalized. In these defects the direction of shunting and the shunt magnitude are determined by the PVR/SVR ratio (Fig. 475.9).

After birth in patients with a large VSD, PVR may remain elevated, delaying the normal postnatal decrease, and thus the size of the left-to-right shunt may initially be limited. Because of normal involution of the media of small pulmonary arterioles, PVR begins to fall in the first few weeks after birth, and the size of the left-to-right shunt then increases. Eventually, a large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during early infancy, PVR is only slightly elevated, and the major contribution to pulmonary hypertension is the large communication allowing exposure of the pulmonary circulation to systemic pressure and the large pulmonary blood flow. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow, pulmonary vascular obstructive disease eventually develops. When the PVR/SVR ratio approaches 1:1, the shunt becomes bidirectional, signs of heart failure abate, and the patient begins to show signs of cyanosis (**Eisenmenger physiology**; see Chapter 482.2), intermittent at first, but then more constant. In rare infants with a large VSD, more often in those with Down syndrome, PVR never decreases after birth, and symptoms may remain minimal until Eisenmenger physiology becomes evident.

The magnitude of intracardiac shunts is usually described by the Qp:Qs ratio. If the left-to-right shunt is small (Qp:Qs <1.5:1), the cardiac chambers are not appreciably enlarged, and the pulmonary vascular bed is probably normal. If the shunt is large (Qp:Qs >2:1), left atrial and LV volume overload occurs, and RV and pulmonary arterial hypertension may be present if the defect is large. The main pulmonary artery, left atrium, and left ventricle are enlarged.

CLINICAL MANIFESTATIONS

The clinical findings of patients with a VSD vary according to the size of the defect and pulmonary blood flow and pressure. Small VSDs with trivial left-to-right shunts and normal pulmonary artery pressure (PAP) are common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. Characteristically, a loud, harsh, or blowing holosystolic murmur is present and heard best over the lower-left sternal border, and it is frequently accompanied by a thrill. In a few cases the murmur ends before the second heart sound (S_2), presumably because of closure of the defect during late systole. A short, loud, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny VSD in the apical muscular septum. These tiny defects most often close during infancy. In premature infants the murmur of a VSD may be heard early because PVR decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for signs of congestive heart failure: dyspnea, feeding difficulties, poor growth, profuse perspiration, and recurrent pulmonary infections in early infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. It is less likely to be prominent in the newborn period before PVR drops. The

pulmonic component of S_2 may be increased as a result of pulmonary hypertension. The presence of a mid-diastolic, low-pitched rumble at the apex is caused by increased blood flow across the mitral valve and usually indicates a Qp:Qs ratio ≥2:1. This murmur is best appreciated with the bell of the stethoscope.

DIAGNOSIS

In patients with small VSDs, the chest radiograph is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The ECG is generally normal but may suggest LV hypertrophy. The presence of RV hypertrophy on ECG is worrisome and a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs the chest radiograph shows gross cardiomegaly with prominence of both ventricles, the left atrium, and the pulmonary artery (Fig. 475.10). Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The ECG shows biventricular hypertrophy; the P waves may be notched (indicative of left atrial [LA] enlargement).

The 2D echocardiogram shows the position and size of the VSD (see Fig. 475.8). In small defects, especially those of the muscular septum, the defect itself may be difficult to image and is visualized only by color Doppler examination. In defects of the **membranous septum**, a thin membrane (called a **ventricular septal aneurysm** but consisting of abnormal tricuspid valve tissue) can partially cover the defect and limit the volume of the left-to-right shunt. Echocardiography is also useful for estimating shunt size by examining the degree of volume overload of the left atrium and left ventricle; in the absence of associated lesions, the extent of their increased dimensions is a good reflection of the size of the left-to-right shunt. Pulsed Doppler examination shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Such calculation allows an estimation of RV pressure and helps determine whether the patient is at risk for the development of early pulmonary vascular disease. The echocardiogram can also be useful to determine the presence of aortic valve insufficiency or aortic leaflet prolapse, which can be associated especially with supracristal VSDs.

The hemodynamics of a VSD can also be demonstrated by cardiac catheterization, although catheterization currently is performed only when laboratory data do not fit well with the clinical findings or when pulmonary vascular disease is suspected. Oximetry demonstrates increased oxygen content in the right ventricle; because some defects eject blood almost directly into the pulmonary artery (streaming), the full magnitude of the oxygen saturation increase may only be apparent when pulmonary arterial blood is sampled. Small, restrictive VSDs are associated with normal right-sided heart pressures and PVR. Large, nonrestrictive VSDs are associated with equal or near-equal pulmonary and systemic systolic pressure and variable elevations in PVR. Pulmonary blood flow may be 2-4 times systemic blood flow. In patients with such "hyperdynamic pulmonary hypertension," PAP is at systemic level, but PVR is only minimally elevated because of the high pulmonary blood flow (resistance is equal to the mean pressure divided by flow). However, if left untreated until Eisenmenger syndrome is present, systolic and diastolic PAP will be elevated and the degree of left-to-right shunting minimal. In these cases, desaturation of blood in the left ventricle is usually encountered. The size, location, and number of ventricular defects can be demonstrated by left ventriculography. Contrast medium passes across the defect(s) to opacify the right ventricle and pulmonary artery. Administration of 100% oxygen with and without nitric oxide can be used to determine whether PVR, if elevated, is still reactive and therefore more likely to decrease after surgical repair.

TREATMENT

The natural course of a VSD depends to a large degree on the size of the defect. A significant number (30–50%) of small defects close spontaneously, most frequently during the first 2 years of life. Small *muscular* VSDs are more likely to close (up to 80%) than *membranous* VSDs (up to 35%). Most defects that close do so before age 4 years, although spontaneous closure has been reported in adults. VSDs that close often have ventricular septal aneurysm (accessory tricuspid valve) tissue covering them that limits the magnitude of the shunt. Most children with small restrictive defects remain asymptomatic, without evidence of an increase in heart size, PAP, or PVR; a long-term risk is infective endocarditis. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. It is recommended that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. However, with the declining risk of open heart surgery, whether all VSDs should be closed electively in mid-childhood is still debated.

It is less common for moderate or large VSDs to close spontaneously, although even defects large enough to result in heart failure may become smaller, and up to 8% may close completely. More frequently, infants with large defects have repeated episodes of respiratory infection and heart failure despite optimal medical management. Heart failure may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. These patients are at risk for pulmonary vascular disease if the defect is not repaired during early infancy.

Patients with VSD are also at risk for the development of **aortic valve regurgitation**, the greatest risk occurring in patients with a supracristal VSD (see Chapter 475.7), where the position of the defect undermines support for the right coronary or noncoronary leaflet of the aortic valve. A small number of patients with VSD develop **acquired infundibular pulmonary stenosis**, which then protects the pulmonary circulation from the short-term effects of pulmonary overcirculation and the long-term effects of pulmonary vascular disease. In these patients the clinical picture changes from that of a VSD with a large left-to-right shunt to a VSD with pulmonary stenosis. The shunt may diminish in

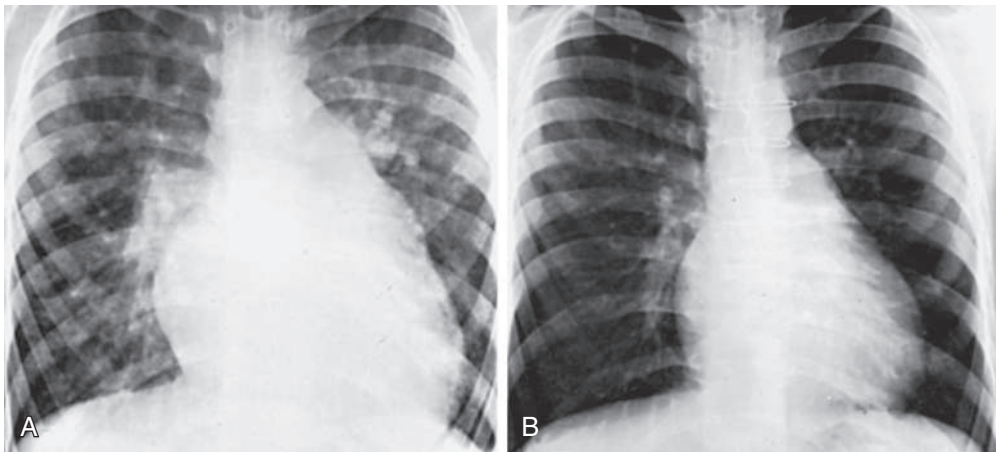

Fig. 475.10 A, Preoperative radiograph in a patient with a ventricular septal defect with a large left-to-right shunt and pulmonary hypertension. Significant cardiomegaly, prominence of the pulmonary arterial trunk, and pulmonary overcirculation are evident. B, Three years after surgical closure of the defect, heart size is greatly decreased and the pulmonary vasculature is normal.

size, become balanced, or even become a net right-to-left shunt. These patients must be carefully distinguished from those in whom an Eisenmenger physiology develops (see Chapter 482.2).

In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is not recommended; however, routine follow-up with the cardiologist is important. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; with the latest revision of the American Heart Association (AHA) guidelines, antibiotic prophylaxis is no longer recommended for dental visits or surgical procedures (see Chapter 486). These patients can be monitored by a combination of clinical examination and noninvasive laboratory tests until the VSD has closed spontaneously. Echocardiography is used to estimate PAP, screen for the development of LVOT pathology (subaortic membrane or aortic regurgitation), and confirm spontaneous closure.

In infants with a large VSD and heart failure, management is directed at reducing symptoms and optimizing the patient's fluid status so that they are in optimal condition for surgical repair. In infants in the first year of life, if early treatment is successful, the size of the defect may sometimes diminish in size with clinical improvement. Selected patients in this group can be observed closely with echocardiographic monitoring. The clinician must be alert not to confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Because surgical closure can be carried out at low risk in most infants, medical management should not be pursued in symptomatic infants after an initial unsuccessful trial. Because pulmonary vascular disease can usually be prevented when surgery is performed within the first year of life, even infants with well-controlled heart failure should not have surgery delayed inordinately unless there is echocardiographic evidence that the defect is becoming pressure restrictive.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically or in whom the defect is not decreasing in size; infants between 6 and 12 months of age with moderate to large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 months with a Qp:Qs ratio greater than 2:1. Patients with a supracristal VSD of any size are usually referred for surgery because of their higher risk for developing aortic valve regurgitation (see Chapter 475.7). Severe pulmonary vascular disease nonresponsive to pulmonary vasodilators is a contraindication to closure of a VSD.

Transcatheter closure has been used successfully in treating larger muscular VSDs, which may be difficult to access by surgery. Perimembranous and intracristal VSD catheter closure is more complex because of the proximity of the defect to the tricuspid valve and conduction system; devices have been designed more specifically to address these issues and are currently being investigated. Preliminary data suggest that, for carefully selected patients (usually children beyond infancy), the results appear to be comparable to surgical repair. Hybrid methods employing a sternotomy with device placement through the anterior wall of the right ventricle under transesophageal echocardiographic and fluoroscopic visualization have also been performed in difficult-to-approach defects.

PROGNOSIS

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or device closure and heart block requiring a pacemaker) are rare. Surgical risks are somewhat higher for defects in the muscular septum, particularly apical defects and multiple (Swiss cheese–type) VSDs. Some of these patients may require pulmonary arterial banding if symptomatic, with subsequent debanding and repair of multiple VSDs at an older age.

After surgical closure of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal (see Fig. 475.10), thrills and murmurs are absent, and pulmonary artery hypertension regresses. The patient's clinical status greatly improves. Most infants begin to thrive, often quite rapidly after hospital discharge, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next year. In some patients, after successful surgery, systolic ejection murmurs of low intensity persist for months. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residua are considered to be at standard risk for health and life insurance.

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475.7 Supracristal Ventricular Septal Defect with Aortic Insufficiency

Daniel Bernstein

A supracristal VSD can be complicated by **prolapse of the aortic valve** into the defect and aortic insufficiency, which may eventually develop in 50–90% of these patients. Although supracristal VSD accounts for approximately 5% of all patients with VSD, the incidence is higher in Asian children and in males. The VSD, which may be small or moderate in size, is located anterior to and directly below the pulmonary valve in the outlet septum, superior to the muscular ridge known as the *crista supraventricularis,* which separates the trabecular body of the right ventricle from the smooth outflow portion. The right or, less often, the noncoronary aortic cusp prolapses into the defect and may partially or even completely occlude it. Such occlusion may limit the amount of left-to-right shunting and give the false impression that the defect is not large. Aortic insufficiency is most often not recognized until after 5 years of age, or even later. Although most common with supracristal VSDs, aortic insufficiency is occasionally associated with VSDs located in the membranous septum.

Early heart failure secondary to a large left-to-right shunt rarely occurs, but without surgery, moderate to severe aortic insufficiency and left ventricular failure may eventually ensue. The murmur of a supracristal VSD is usually heard at the mid- to upper-left sternal border, as opposed to the lower-left sternal border, and it is sometimes confused with that of pulmonic stenosis. A decrescendo diastolic murmur will be appreciated at the upper-right or mid-left sternal borders if there is aortic insufficiency. More advanced degrees of aortic insufficiency will be associated with a wide pulse pressure and a hyperdynamic precordium. These clinical findings must be distinguished from PDA or other defects associated with aortic runoff.

The clinical manifestations vary widely, from trivial aortic regurgitation and small left-to-right shunts in asymptomatic children to florid aortic insufficiency and massive cardiomegaly in symptomatic adolescents. Closure of all supracristal ventricular VSDs is usually recommended to prevent the development of aortic regurgitation, even in an asymptomatic child. Patients who already have significant aortic insufficiency require surgical intervention to prevent irreversible left ventricular dysfunction. Surgical options depend on the degree of damage to the valve, and for mild insufficiency, may include simple closure of the defect to bolster the valve apparatus without touching the valve itself, valvuloplasty for more significant degrees of involvement, and replacement with a prosthesis or homograft or aortopulmonary translocation (Ross procedure) for severe involvement.

475.8 Patent Ductus Arteriosus

Daniel Bernstein

During fetal life, most of the pulmonary arterial blood is shunted right to left through the ductus arteriosus into the aorta (see Chapter 470). Functional closure of the ductus normally occurs soon after birth, usually within the first week of life, but if the ductus remains patent when

PVR falls, aortic blood then is shunted left to right into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female patients with patent ductus arteriosus (PDA) outnumber males 2:1. PDA is also associated with maternal rubella infection during early pregnancy, an uncommon occurrence in the vaccination era. PDA is a common problem in premature infants because the smooth muscle in the wall of the preterm ductus is less responsive to high Po_2 and therefore less likely to constrict after birth. In these infants the shunt through a PDA can cause severe hemodynamic derangements and several major sequelae (see Chapter 131.3).

When a term infant is found to have a PDA, the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media, whereas in the premature infant, the PDA usually has a normal structure. Thus a PDA persisting beyond the first few weeks of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10% of patients with other congenital heart lesions and often plays a critical role in providing a source of pulmonary blood flow when the right ventricular outflow tract is stenotic or atretic (see Chapter 479) or in providing systemic blood flow in the presence of aortic coarctation or interruption (see Chapters 476.6-476.8) or in hypoplastic left heart syndrome.

A PDA is a common finding (~90%) in patients with **smooth muscle dysfunction syndrome (SMDS)** caused by a heterozygous pathogenic variant in *ACTA2*. Additional features include congenital mydriasis, pulmonary hypertension, aortic and other arterial aneurysms, moyamoya-like cerebrovascular disease, and intestinal hypoperistalsis.

PATHOPHYSIOLOGY

Because of the higher aortic pressure postnatally, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the PVR/SVR ratio. If the PDA is small, pressures within the pulmonary artery, the right ventricle, and the right atrium are normal. If the PDA is large, PAP may be elevated to systemic levels during both systole and diastole. Thus patients with a large PDA are at high risk for the development of pulmonary vascular disease if left unoperated.

CLINICAL MANIFESTATIONS

A small PDA is usually asymptomatic and is usually diagnosed by the presence of a heart murmur. A large PDA will result in heart failure similar to that encountered in infants with a large VSD. Stunting of physical growth may be a major manifestation in infants with large shunts. A small PDA is associated with normal peripheral pulses, and a large PDA results in bounding peripheral arterial pulses and a *wide pulse pressure,* caused by runoff of blood into the pulmonary artery during diastole. Although normal in size when the ductus is small, the heart is moderately or grossly enlarged in cases with a large communication; in these patients the apical impulse is prominent and, with cardiac enlargement, is heaving. A **thrill**, maximal in the second left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex. It is usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as "machinery-like" in quality. It begins soon after onset of S_1, reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the second left intercostal space or radiate down the left sternal border or to beneath the left clavicle. When PVR is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

DIAGNOSIS

If the left-to-right shunt is small, the ECG is normal; if the ductus is large, LV or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when RV hypertrophy is present on the ECG.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased pulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to greatly enlarged. The chambers involved are the left atrium and left ventricle. The aortic knob may be normal or prominent.

On echocardiogram the cardiac chambers will be normal in size if the ductus is small. With large shunts, LA and LV dimensions are increased. The ductus can easily be visualized directly and its size estimated. Color and pulsed Doppler examinations demonstrate systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery and aortic retrograde flow in diastole in the presence of a large shunt (Fig. 475.11).

The clinical signs and echocardiographic findings are sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In rare patients with atypical findings, cardiac catheterization may be indicated for confirmation of diagnosis. Cardiac catheterization will demonstrate either normal or increased pressure in the right ventricle and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms the left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Other conditions can produce systolic and diastolic murmurs in the pulmonic area in an acyanotic patient (see Chapter 471). An **aortico-pulmonary window defect** may rarely be clinically indistinguishable from a patent ductus, although in most cases the murmur is only systolic and is loudest at the right rather than the left upper sternal border

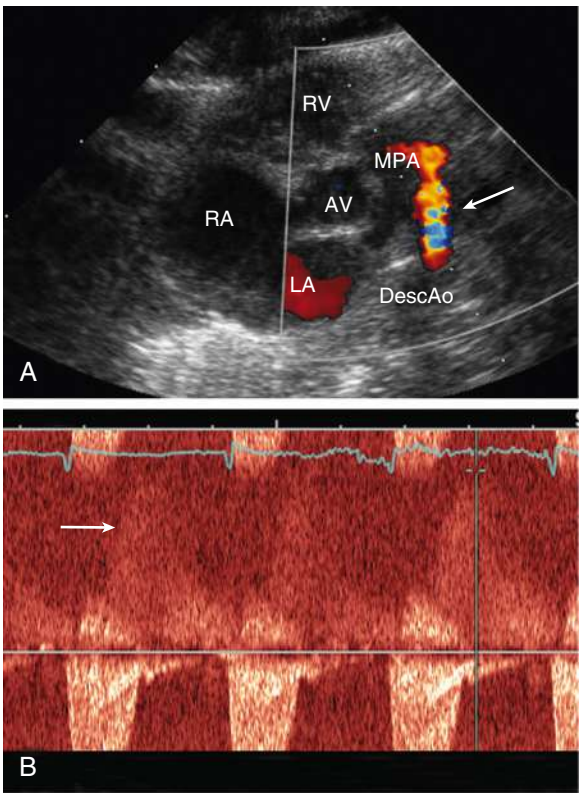

Fig. 475.11 Echocardiogram in a newborn with a small to moderate-size patent ductus arteriosus. **A,** Color Doppler evaluation in a parasternal short-axis view shows flow *(arrow)* from the aorta into the main pulmonary artery. **B,** Doppler evaluation demonstrates retrograde diastolic flow into the pulmonary artery. AV, Aortic valve; DescAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

(see Chapter 475.9). A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, a coronary AV fistula, and an aberrant left coronary artery with massive collaterals from the right coronary display dynamics similar to that of a PDA with a continuous murmur and a wide pulse pressure. Truncus arteriosus with torrential pulmonary flow also can present with aortic runoff physiology. A peripheral AV fistula also results in a wide pulse pressure, but the distinctive precordial murmur of a PDA is not present. VSD with aortic insufficiency, repaired tetralogy of Fallot, and combined aortic and mitral insufficiency (usually from rheumatic fever) may be confused with a PDA, but the murmurs should be differentiated by their to-and-fro rather than continuous nature. In a to-and-fro murmur there is a quiet segment between the systolic and diastolic components, whereas in a continuous murmur there is flow disturbance throughout the cardiac cycle (even if the murmur is louder during systole than diastole). The combination of a large VSD and a PDA result in findings more like those of an isolated VSD. Echocardiography should be able to eliminate these other diagnostic possibilities.

PROGNOSIS AND COMPLICATIONS

Spontaneous closure of the ductus after infancy is extremely rare. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. In patients with a large PDA, cardiac failure most often occurs in early infancy but may occur later in life, even with a moderate-sized communication.

Infective endarteritis may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications include aneurysmal dilation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo ductal closure (see Chapter 482.2).

TREATMENT

Irrespective of age, patients with a PDA require either catheter or surgical closure. In patients with a small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In patients with a moderate to large PDA, closure is accomplished to treat heart failure and prevent the development of pulmonary vascular disease. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted.

Transcatheter PDA closure is routinely performed in the cardiac catheterization laboratory (Fig. 475.12). Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with an umbrella-like or pluglike device or with a catheter-introduced sac into which several coils are released. Surgical closure of a PDA can be accomplished by a standard left thoracotomy or using thoracoscopic minimally invasive techniques. The case fatality rate with interventional or surgical treatment is considerably less than 1%; thus closure of the ductus is indicated even in asymptomatic patients. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of cardiac failure rapidly disappear. Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. A functional systolic murmur over the pulmonary area may persist; it may represent turbulence in a persistently dilated pulmonary artery. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over several months, and the ECG becomes normal.

PATENT DUCTUS ARTERIOSUS IN LOW BIRTHWEIGHT INFANTS

See Chapter 126.1.

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475.9 Aortopulmonary Window Defect

Daniel Bernstein

An aortopulmonary window defect consists of a communication between the ascending aorta and the main pulmonary artery. The presence of pulmonary and aortic valves and an intact ventricular septum distinguishes this anomaly from **truncus arteriosus** (see Chapter 480.8). An aortopulmonary window is an associated lesion in patients with **smooth muscle dysfunction syndrome** (see Chapter 475.8). Symptoms of heart failure appear during early infancy; occasionally, minimal cyanosis is present. The defect is usually large, and the cardiac murmur is usually systolic with an apical mid-diastolic rumble as a result of the increased blood flow across the mitral valve. In the rare instance when the communication is smaller and pulmonary hypertension is absent, the findings on examination can mimic those of a PDA (wide pulse pressure and a continuous murmur at the upper sternal borders). The ECG shows either LV or biventricular hypertrophy. Radiographic studies demonstrate cardiac enlargement and prominence of the pulmonary artery and intrapulmonary

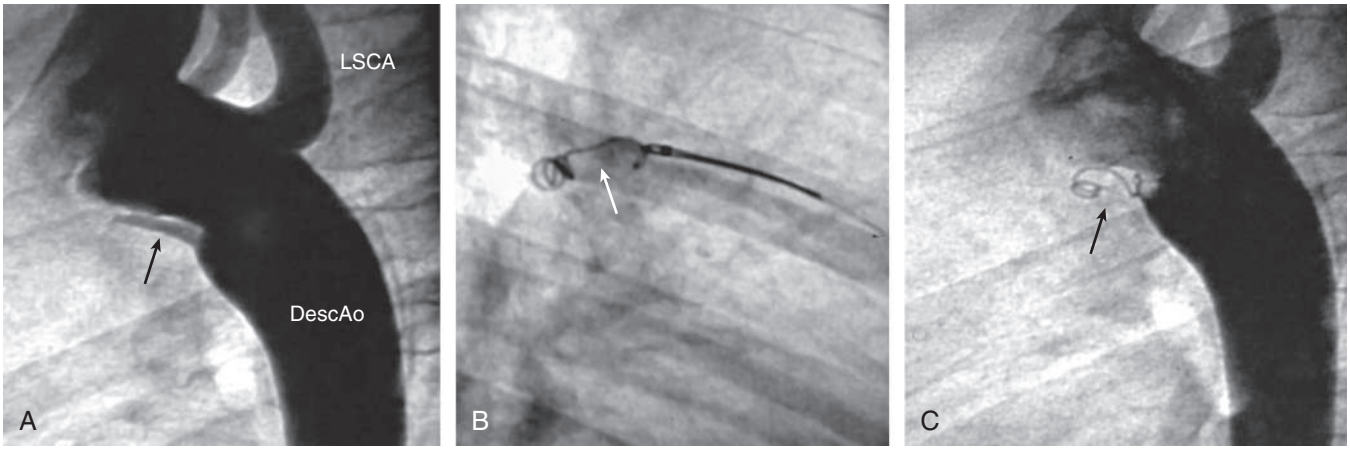

Fig. 475.12 Transcatheter closure of a small patent ductus arteriosus using a coil. **A,** Angiogram of transverse and descending aorta shows small PDA *(arrow).* **B,** Coil *(arrow)* has been extruded from the sheath and is being positioned in the ductal lumen. **C,** Angiogram demonstrating total occlusion of PDA by coil *(arrow).* DescAo, Descending aorta; LSCA, left subclavian artery.

vasculature. The echocardiogram shows enlarged left-sided heart chambers; the window defect can best be delineated with color flow Doppler. CT or MR angiography can also be used to visualize the defect (see Fig. 472.26).

Cardiac catheterization, usually performed in older children to evaluate pulmonary vascular resistance, reveals a left-to-right shunt at the level of the pulmonary artery, as well as hyperkinetic pulmonary hypertension, because the defect is almost always large. Selective aortography with injection of contrast medium into the ascending aorta demonstrates the lesion, and manipulation of the catheter from the main pulmonary artery directly to the ascending aorta is also diagnostic.

An aortopulmonary window defect is surgically corrected during infancy. If surgery is not carried out in infancy, survivors carry the risk of progressive pulmonary vascular obstructive disease, similar to that of other patients who have large intracardiac or great vessel communications.

475.10 Coronary Artery Fistula

Daniel Bernstein

A congenital fistula may exist between a coronary artery and an atrium, ventricle (especially the right), or pulmonary artery. Sometimes, multiple fistulas exist. Regardless of the recipient chamber, the clinical signs are similar to those of PDA, although the machinery-like murmur may be more diffuse. If the flow is substantial, the involved coronary artery may be dilated or aneurysmal. The anatomic abnormality is usually demonstrable by color flow Doppler echocardiography and, during catheterization, by contrast injection into the ascending aorta. Small fistulas may be hemodynamically insignificant and may even close spontaneously. If the shunt is large, treatment consists of either transcatheter coil embolization or, for lesions not amenable to catheter intervention, surgical closure of the fistula.

475.11 Ruptured Sinus of Valsalva Aneurysm

Daniel Bernstein

When one of the sinuses of Valsalva of the aorta is weakened by congenital or acquired disease, an aneurysm may form and eventually rupture, usually into the right atrium or ventricle. This condition is rare in childhood. The onset is usually sudden. The diagnosis should be suspected in a patient in whom symptoms of acute heart failure develop in association with a new, loud, to-and-fro murmur. Color Doppler echocardiography and cardiac catheterization demonstrate the left-to-right shunt at the atrial or ventricular level. Urgent surgical repair is generally required. This condition is often associated with infective endocarditis of the aortic valve.

Chapter 476
Acyanotic Congenital Heart Disease: Obstructive Lesions

476.1 Pulmonary Valve Stenosis with Intact Ventricular Septum

Daniel Bernstein

Of the various forms of right ventricular (RV) outflow obstruction with an intact ventricular septum, the most common is isolated **valvular pulmonary stenosis**, which accounts for 7–10% of all congenital heart defects. The valve cusps are deformed to various degrees and, as a result, the valve opens incompletely during systole. The valve may be bicuspid or tricuspid and the leaflets partially fused together with an eccentric outlet. This fusion may be so severe that only a pinhole central opening remains. If the valve is not severely thickened, it produces a domelike obstruction to RV outflow during systole. Isolated infundibular or subvalvular stenosis, supravalvular pulmonary stenosis, and branch pulmonary artery stenosis are also encountered. In cases where pulmonary valve stenosis is associated with a **ventricular septal defect** (VSD) but without anterior deviation of the infundibular septum and overriding aorta, this condition is better classified as pulmonary stenosis with VSD rather than as **tetralogy of Fallot** (see Chapter 479.1). Pulmonary stenosis and an **atrial septal defect** (ASD) are also occasionally seen as associated defects.

The clinical and laboratory findings reflect the dominant lesion, but it is important to rule out any associated anomalies. Pulmonary stenosis as a result of valve dysplasia is the most common cardiac abnormality in **Noonan syndrome** (see Chapter 101.1) and is associated, in approximately 50% of cases, with a pathogenic variant in *PTPN11,* encoding the protein tyrosine phosphatase SHP-2 on chromosome 12. *SOS1* gene variants cause an additional 10–15%, and *RAF1* and *RIT1* genes each account for about 5% of cases. These genes are components of the RAS/MAPK cell signaling pathway, important for cell division; however, the mechanism by which these gene changes cause pulmonic stenosis is unknown. Pulmonary stenosis can also be a component of **LEOPARD syndrome** (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness syndrome), often associated with hypertrophic cardiomyopathy. Pathogenic variants in *PTPN11, RAF1, BRAF,* and *MAP2K1* have been implicated in LEOPARD syndrome. Pulmonary stenosis, of the valve or more commonly of the branch pulmonary arteries, is a common finding in patients with arteriohepatic dysplasia, also known as **Alagille syndrome** (see Chapter 404); pathogenic variants have been found in *JAGGED1* or *NOTCH2,* components of the Notch signaling pathway.

PATHOPHYSIOLOGY

The obstruction to outflow from the right ventricle to the pulmonary artery results in increased RV systolic pressure and wall stress, which lead to hypertrophy of the right ventricle (Fig. 476.1). The severity of these abnormalities depends on the size of the restricted valve opening. In severe cases, RV pressure may be higher than systemic arterial systolic pressure, whereas with milder obstruction, RV pressure is only mildly or moderately elevated. Pulmonary artery pressure (PAP, distal to the obstruction) is either normal or decreased. Arterial oxygen saturation will be normal even in cases of severe stenosis, unless an intracardiac communication such as a VSD or ASD is allowing blood to shunt from right to left. However, when severe pulmonic stenosis occurs in a neonate, decreased RV compliance often leads to cyanosis as a result of right-to-left shunting through a **patent foramen ovale** (PFO), a condition termed **critical pulmonic stenosis**.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with mild or moderate stenosis usually have no symptoms. Growth and development are most often normal. If the stenosis is severe, signs of RV failure such as hepatomegaly, peripheral edema, and exercise intolerance may be present. In a neonate or young infant with critical pulmonic stenosis, signs of RV failure may be more prominent; cyanosis is often present because of right-to-left shunting at the foramen ovale.

With **mild pulmonary stenosis**, central venous pressure is normal. The heart is not enlarged, the apical impulse is normal, and the RV impulse is not palpable. A sharp pulmonic ejection click (caused by doming of the valve) is heard immediately after the first heart sound (S_1) at the left upper sternal border and over the sternum, more prominently during expiration. The second heart sound (S_2) is split, with a pulmonary component of normal intensity that may be slightly

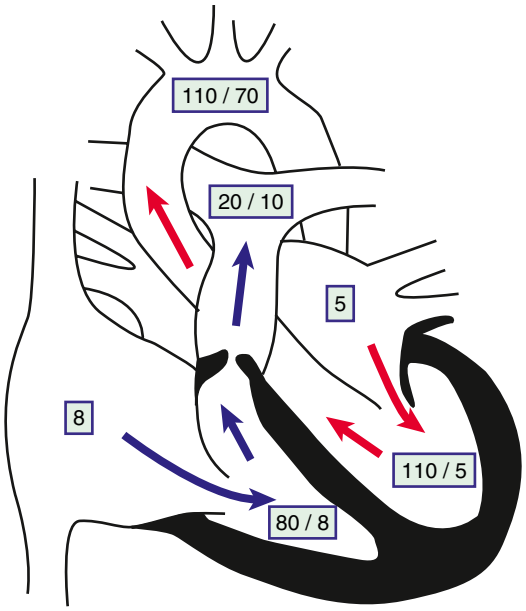

Fig. 476.1 Physiology of valvular pulmonary stenosis. *Boxed numbers* represent pressure in mm Hg. Because of the absence of right-to-left or left-to-right shunting, blood flow through all cardiac chambers is normal at 3 L/min/m^2. The pulmonary-to-systemic blood flow ratio (Qp:Qs) is 1:1. Right atrial pressure is increased slightly as a result of decreased right ventricular compliance. The right ventricle is hypertrophied, and systolic and diastolic pressures are increased. The pressure gradient across the thickened pulmonary valve is 60 mm Hg. The main pulmonary artery pressure is slightly low, and poststenotic dilation is present. Left-sided heart pressure is normal. Unless right-to-left shunting is occurring through a foramen ovale, the patient's systemic oxygen saturation will be normal.

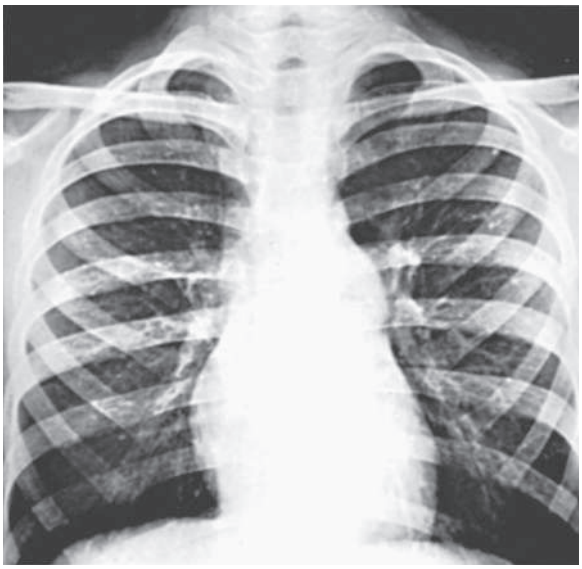

Fig. 476.2 Radiograph of patient with valvular pulmonary stenosis and normal aortic root. The heart size is within normal limits, but poststenotic dilation of the pulmonary artery is present.

delayed. A relatively short, low- or medium-pitched systolic ejection murmur is maximally audible over the pulmonic area at the upper left sternal border and radiates minimally to the lung fields bilaterally. The electrocardiogram (ECG) is either normal or shows mild **right ventricular hypertrophy** (RVH) (e.g., slightly increased voltages in the right precordial leads); inversion of the T waves in the right precordial leads may be the only finding. Note that the T wave in lead V_1 should normally be inverted after the first week of life until at least 6-8 years of age. Therefore a positive T wave in V_1 in a young child is a sign of RVH even in the absence of voltage criteria. The only abnormality demonstrable radiographically is usually poststenotic dilation of the pulmonary artery. Two-dimensional (2D) echocardiography shows RVH and a slightly thickened pulmonic valve, which domes in systole. Doppler studies demonstrate a right ventricle–to–pulmonary artery (RV-PA) pressure gradient of ≤30 mm Hg.

In **moderate pulmonic stenosis**, central venous pressure may be slightly elevated; in older children, a prominent *a* wave may be noted in the jugular pulse. An RV lift may be palpable at the lower-left sternal border. S_2 is split, with a delayed and soft pulmonic component. As valve motion becomes more limited with more severe degrees of stenosis, both the pulmonic ejection click and the pulmonic S_2 may become inaudible. With increasing degrees of stenosis, the systolic ejection murmur becomes louder and harsher (higher frequency), the peak of the murmur is prolonged later into systole, and the murmur radiates more prominently to both lung fields, heard best over the back.

The ECG reveals RVH, sometimes with a prominent spiked P wave. Radiographically, the heart can vary from normal size to mildly enlarged with uptilting of the apex because of the prominence of the right ventricle; pulmonary vascularity is usually normal or slightly decreased. The echocardiogram shows a thickened pulmonic valve with restricted systolic motion. Doppler examination demonstrates an RV-PA pressure gradient of 30-60 mm Hg. Mild tricuspid regurgitation may be present and allows for Doppler confirmation of RV systolic pressure.

In **severe pulmonary stenosis**, mild to moderate cyanosis may be noted in patients with an interatrial communication (ASD or PFO). In the absence of any intracardiac shunt, cyanosis is absent. Hepatic enlargement and peripheral edema, if present, are an indication of RV failure. Elevation of central venous pressure is common and is identified as a large presystolic jugular *a* wave. The heart is moderately or greatly enlarged, and a conspicuous parasternal RV lift is present and frequently extends to the left midclavicular line. The pulmonic component of S_2 is usually inaudible. A loud, long, and harsh systolic ejection murmur, usually accompanied by a thrill, is maximally audible in the pulmonic area and may radiate over the entire precordium, to both lung fields, and to the back. The peak of the murmur occurs later in systole as valve opening becomes more restricted. The murmur frequently encompasses the aortic component of S_2 but is not preceded by an ejection click.

The ECG shows marked RVH, frequently accompanied by a tall, spiked P wave. Radiographic studies confirm the presence of cardiac enlargement with prominence of the right ventricle and right atrium. Prominence of the main pulmonary artery (MPA) segment may be seen as a sign of poststenotic dilation (Fig. 476.2). Intrapulmonary vascularity is decreased. The 2D echocardiogram shows severe deformity of the pulmonary valve and RVH (Fig. 476.3). In the late stages of the disease, systolic dysfunction of the right ventricle may be seen, and in these cases the ventricle becomes dilated, with prominent tricuspid regurgitation. Doppler studies demonstrate a high gradient (>60 mm Hg) across the pulmonary valve. The classic findings of severe pulmonary stenosis in older children are rarely seen today because of early intervention. In the newborn period, signs of critical pulmonic stenosis are accompanied by cyanosis.

Cardiac catheterization is not generally required for diagnostic purposes but is undertaken to perform a therapeutic **balloon valvuloplasty** procedure. Catheterization demonstrates an abrupt pressure gradient across the pulmonary valve. PAP is either normal or low. The severity of the stenosis is graded based on the ratio of RV systolic pressure to systemic systolic pressure or the RV-PA pressure gradient: 10-30 mm Hg in mild cases, 30-60 mm Hg in moderate cases, and >60 mm Hg or with RV pressure greater than systemic pressure in severe cases. If cardiac output is low or a significant right-to-left shunt exists across the atrial septum, the pressure gradient may underestimate the degree of valve stenosis. Selective right ventriculography demonstrates the

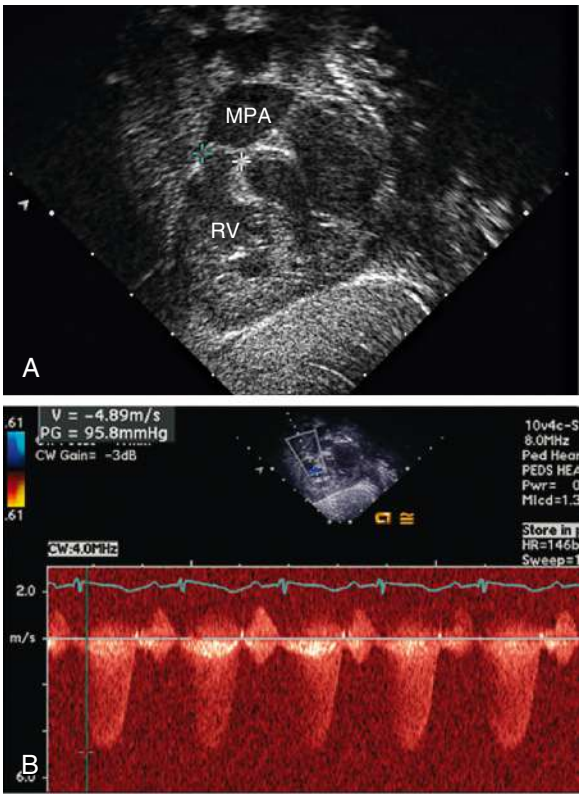

Fig. 476.3 Echocardiogram demonstrating valvar pulmonic stenosis. A, Subcostal view showing thickened pulmonary valve leaflets *(between crosshatches)*. B, Doppler study indicating a 95 mm Hg peak pressure gradient across the stenotic valve. MPA, Main pulmonary artery; RV, right ventricle.

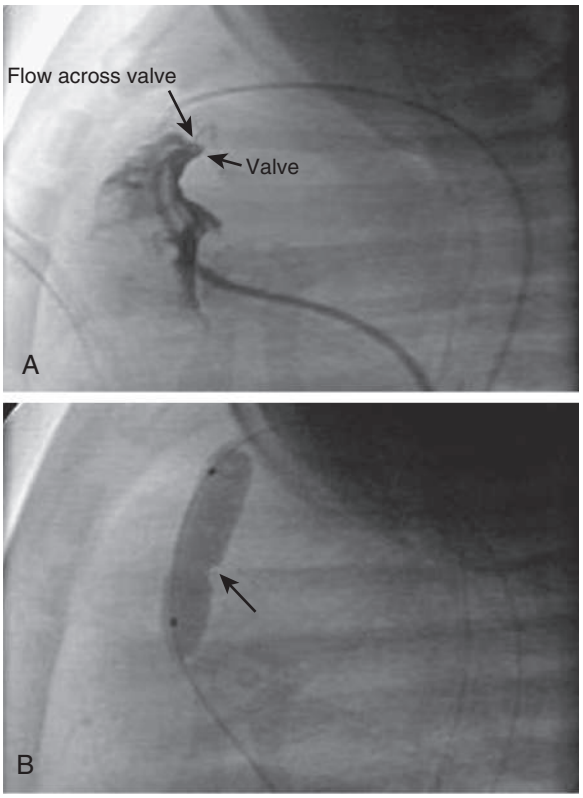

Fig. 476.4 Valvar pulmonary stenosis and balloon valvuloplasty. A, Right ventricular angiogram showing severely stenotic pulmonary valve with narrow jet of blood flowing across. B, Inflation of the balloon catheter showing the indentation *(arrow)* made on the balloon from the stenotic valve. *(Photos courtesy Dr. Jeffrey Feinstein, Stanford University, Stanford, CA.)*

thickened, poorly mobile valve. In mild to moderate stenosis, doming of the valve in systole is readily seen. Flow of contrast medium through the stenotic valve in ventricular systole produces a narrow jet of dye that fills the dilated MPA. Subvalvular hypertrophy may be present and may intensify the obstruction.

TREATMENT

Patients with moderate or severe isolated pulmonary stenosis require relief of the obstruction. Balloon valvuloplasty is the initial treatment of choice for the majority of patients (Fig. 476.4). Patients with severely thickened pulmonic valves, especially common in those with **Noonan syndrome**, may require surgical intervention. In a neonate with critical pulmonic stenosis and cyanosis, urgent treatment by either balloon valvuloplasty or surgical valvotomy is warranted.

Excellent results are obtained in most patients. The gradient across the pulmonary valve is greatly reduced or abolished. In the early period after balloon valvuloplasty, a small to moderate residual gradient may remain because of muscular infundibular narrowing; it usually resolves with time. A short, early decrescendo diastolic murmur may be heard at the midsternal to upper left sternal border as a result of pulmonary valvular insufficiency. The degree of insufficiency is usually not clinically significant, although it can occasionally worsen over time as the child grows. No difference in patient status after valvuloplasty or surgery has been noted at late follow-up; recurrence is unusual after successful treatment except in those patients with extremely dysplastic valves. In the small minority of patients where the degree of **pulmonary regurgitation** is more severe, RV dilation may ensue, and these patients require careful follow-up and may require surgical intervention (repair or valve replacement) or placement of a transcatheter stent-valve (e.g., Melody or Harmony valve).

PROGNOSIS AND COMPLICATIONS

Heart failure occurs only in severe cases and most often during the first month of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is almost exclusively seen in the neonatal period when the stenosis is severe. Infective endocarditis is a risk but is not common in childhood.

Children with mild stenosis can lead a normal life, but their progress should be evaluated at regular intervals. Patients who have small gradients rarely show progression and do not need intervention, but a significant gradient is more likely to develop in children with moderate stenosis as they grow older. Worsening of obstruction over time may also be caused by the development of secondary subvalvular muscular hypertrophy. In untreated severe stenosis, the course may abruptly worsen with the development of RV dysfunction and cardiac failure. Infants with critical pulmonic stenosis require urgent catheter balloon valvuloplasty or surgical valvotomy. Development of RV failure many years after pulmonary balloon valvuloplasty is uncommon. Nonetheless, patients should be followed serially for worsening pulmonary insufficiency and RV dilation.

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476.2 Infundibular Pulmonary Stenosis and Double-Chamber Right Ventricle

Daniel Bernstein

Infundibular pulmonary stenosis is caused by muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an

infundibular chamber may be present between the right ventricular cavity and the pulmonary valve. In many cases, a VSD may have been present initially and later closed spontaneously. When the pulmonary valve is also stenotic, the combined defect is primarily classified as valvular stenosis with secondary infundibular hypertrophy. The hemodynamics and clinical manifestations of patients with isolated infundibular pulmonary stenosis are similar, for the most part, to those described for isolated valvular pulmonary stenosis (see Chapter 476.1).

A common variation in RV outflow obstruction below the pulmonary valve is that of a **double-chambered right ventricle**. In this condition, a muscular band is present in the mid-RV region; the band divides the chamber into two parts and creates obstruction between the inlet and outlet portions. An associated VSD is often noted, and these may close spontaneously. Obstruction is not usually seen early in life but may progress rapidly in a similar manner to the progressive infundibular obstruction observed with tetralogy of Fallot (see Chapter 479.1).

The diagnosis of isolated RV infundibular stenosis or double-chambered right ventricle is usually made by echocardiography. The ventricular septum must be evaluated carefully to determine whether an associated VSD is present. When the obstruction is moderate to severe, surgery is indicated. After surgery, the pressure gradient is abolished or greatly reduced, and the long-term outlook is excellent.

476.3 Pulmonary Stenosis in Combination with an Intracardiac Shunt

Daniel Bernstein

Valvular or infundibular pulmonary stenosis, or both, may be associated with either an ASD or a VSD. In these patients the clinical features depend on the degree of pulmonary stenosis, which determines whether the net shunt is from left to right or from right to left. Neonates with severe pulmonary stenosis (termed **critical pulmonary stenosis**) usually have right-to-left shunting through the foramen ovale (see Chapter 476.1).

The presence of a large left-to-right shunt at the atrial or ventricular level is evidence that the pulmonary stenosis is mild. These patients have symptoms similar to those of patients with an isolated ASD or VSD. With increasing age, worsening of the RV outflow obstruction may limit the shunt and result in a gradual improvement in symptoms. Eventually, particularly in patients with pulmonary stenosis and VSD, a further increase in obstruction may lead to right-to-left shunting and cyanosis. When a patient with a VSD has evidence of decreasing heart failure and increased RV forces on the ECG, one must differentiate between the development of increasing pulmonary stenosis vs the onset of pulmonary vascular disease (**Eisenmenger syndrome**; see Chapter 482.2).

These anomalies are readily repaired surgically. Defects in the atrial or ventricular septum are closed, and the pulmonary stenosis is relieved by resection of infundibular muscle or pulmonary valvotomy, or both, as indicated. Patients with a predominant right-to-left shunt can have symptoms similar to those of patients with tetralogy of Fallot (see Chapter 479.1).

476.4 Peripheral Pulmonary Stenosis

Daniel Bernstein

Single or multiple constrictions may occur anywhere along the major branches of the pulmonary arteries and may range from mild to severe and from localized to extensive. Frequently, these defects are associated with other types of congenital heart disease, including valvular pulmonic stenosis, tetralogy of Fallot, patent ductus arteriosus (PDA), VSD, ASD, and supravalvular aortic stenosis. A familial tendency has been recognized in some patients with peripheral pulmonic stenosis. Peripheral pulmonary stenosis is a common cardiac sequelae of congenital rubella syndrome. The combination of supravalvular aortic stenosis with pulmonary arterial branch stenosis, idiopathic hypercalcemia of infancy, elfin facies, and intellectual disability is known as **Williams syndrome**, a condition associated with hemizygous microdeletion of ~25-27 genes (Williams-Beuren syndrome critical region: WBSCR1), including *ELN, LIMK1, GTF21,* and *GTF21RD1* in region 7q11.23 on chromosome 7. Peripheral pulmonary stenosis is also associated with **Alagille syndrome**, which may be associated with a pathogenic variant in the *JAGGED1* or *NOTCH2* genes.

A mild constriction has little effect on the pulmonary circulation. With multiple severe constrictions, pressure is increased in the right ventricle and in the pulmonary artery proximal to the site of obstruction. When the anomaly is isolated, the diagnosis is suspected by the presence of murmurs in widespread locations over the chest, either anteriorly or posteriorly. These murmurs are usually systolic ejection in quality but may be continuous. Most often, the physical signs are dominated by the associated anomaly, such as valvar pulmonary stenosis or tetralogy of Fallot (see Chapter 479.1).

In the immediate newborn period, a mild and transient form of peripheral pulmonic stenosis may be present. Physical findings are generally limited to a soft systolic ejection murmur, which can be heard over either or both lung fields. It is the absence of other physical findings of valvular pulmonic stenosis (RV lift, soft pulmonic S_2, systolic ejection click, murmur loudest at upper left sternal border) that supports this diagnosis. This murmur usually disappears by age 1-2 months.

If the stenosis is severe, the ECG shows evidence of RVH and right atrial hypertrophy, and the chest radiograph shows cardiomegaly and prominence of the MPA. The pulmonary vasculature is usually normal; in some cases, small intrapulmonary vascular shadows are seen that represent areas of poststenotic dilation. Echocardiography is limited in its ability to visualize the distal branch pulmonary arteries. Doppler examination demonstrates the acceleration of blood flow through the stenoses and, if tricuspid regurgitation is present, allows an estimation of RV systolic pressure. MRI and CT are extremely helpful in delineating distal obstructions. If moderate to severe disease is suspected, the diagnosis is usually confirmed by cardiac catheterization.

Severe obstruction of the MPA and its primary branches can be relieved during corrective surgery for associated lesions such as the tetralogy of Fallot or valvular pulmonary stenosis. If peripheral pulmonic stenosis is isolated, it may be treated by catheter balloon dilation, sometimes with placement of an intravascular stent (see Fig. 472.31).

476.5 Aortic Stenosis

Daniel Bernstein

Congenital aortic stenosis accounts for approximately 5% of cardiac malformations recognized in childhood and is more frequent in males (3:1). A bicuspid aortic valve (BAV) is one of the most common congenital heart lesions overall, identified in 1–2% of adults. If isolated, it is not even counted in the overall incidence (0.8% of live births) of congenital heart disease. There is a high incidence of family clustering, with multiple individuals affected with BAV or other left-sided heart lesions. BAV may be encountered in conjunction with other left-sided heart lesions (coarctation of the aorta, aortopathy, mitral stenosis, **Shone complex**, and hypoplastic left heart syndrome) or in conjunction with syndromes such as Loeys-Dietz, Down, Turner, and velocardiofacial (DiGeorge). Several genes have been implicated in BAV, including *NOTCH1, GATA4, GATA5,* and *SMAD6.*

In the most common form, **valvular aortic stenosis**, the leaflets are thickened and the commissures are fused to varying degrees. Left ventricular (LV) systolic pressure is increased as a result of the obstruction to outflow. The LV wall hypertrophies in compensation; as its compliance decreases, end-diastolic pressure increases as well, impairing ventricular filling in the more severe cases.

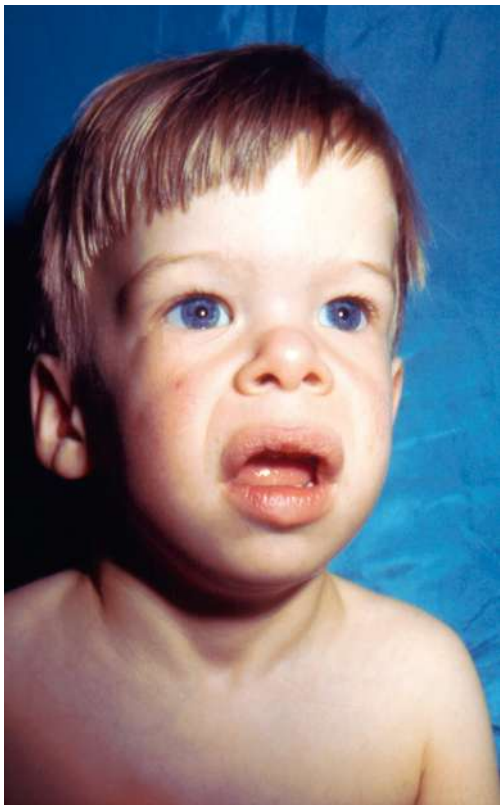

Fig. 476.5 Williams syndrome. *(From Jones KL, Smith DW. The Williams elfin facies syndrome: a new perspective. J Pediatr. 1975;86:718.)*

Subvalvular (subaortic) stenosis with a discrete fibromuscular shelf (subaortic membrane) below the aortic valve is also an important form of left ventricular outflow tract (LVOT) obstruction. This lesion is frequently associated with other forms of congenital heart disease such as mitral stenosis and coarctation of the aorta **(Shone complex)** and may progress in severity with age, sometimes rapidly. Subvalvular aortic stenosis may also become apparent after successful surgery for other congenital heart defects (coarctation of the aorta, PDA, VSD), may develop in association with mild lesions that have not been surgically repaired, or may occur as an isolated abnormality. Subvalvular aortic stenosis may also be caused by a markedly hypertrophied ventricular septum in association with hypertrophic cardiomyopathy (see Chapter 488.2).

Supravalvular aortic stenosis, the least common type, may be sporadic, familial, or associated with **Williams syndrome**, which includes developmental delay (IQ range: 41-80), elfin facies (full face, broad forehead, flattened bridge of the nose, long upper lip, and rounded cheeks) (Fig. 476.5), and idiopathic hypercalcemia of infancy. Additional features include loquacious personality, hypersensitivity to sound, spasticity, hypoplastic nails, dental anomalies (partial anodontia, microdontia enamel hypoplasia), joint hypermobility, nephrocalcinosis, hypothyroidism, and poor weight gain. Narrowing of the coronary artery ostia can occur in patients with supravalvar aortic stenosis and should be carefully evaluated. Stenosis of other arteries, particularly the branch pulmonary arteries, may also be present. Williams syndrome is caused by hemizygous microdeletion of ~25 genes in the WBSCR1 at 7q11.23 on chromosome 7 (see Chapter 476.2).

CLINICAL MANIFESTATIONS

Symptoms in patients with aortic stenosis depend on the severity of the obstruction. Severe aortic stenosis that occurs in early infancy is termed **critical aortic stenosis** and is associated with LV failure and signs of low cardiac output. Heart failure, cardiomegaly, and pulmonary edema are severe, the pulses are weak in all extremities, and the skin may be pale or grayish. Urine output may be diminished. If cardiac output is significantly decreased, the intensity of the murmur at the right upper sternal border may be minimal. The endocardial surface may be fibrotic and stiff (endocardial fibroelastosis) in the most severe cases.

Outside of the newborn period, most infants and children with less severe forms of aortic stenosis remain asymptomatic and display normal growth and development. The murmur is usually discovered during routine physical examination. Rarely, fatigue, chest pain, dizziness, or syncope with exercise may develop in an older child with previously undiagnosed severe obstruction to LV outflow. Sudden death has been reported with aortic stenosis but usually occurs in patients with severe LVOT obstruction in whom the diagnosis and surgical relief have been delayed.

The physical findings are dependent on the degree of obstruction to LV outflow. In mild stenosis, the pulses, heart size, and apical impulse are all normal. With increasing degrees of severity, the pulses become diminished in intensity and the heart may be enlarged, with an LV apical thrust. Mild to moderate valvular aortic stenosis is usually associated with an early systolic ejection click, best heard at the left sternal border and over the sternum. Unlike the click in pulmonic stenosis, its intensity does not vary with respiration. Clicks are unusual in more severe aortic stenosis or in discrete subaortic stenosis. If the stenosis is severe, S_1 may be diminished because of decreased compliance of the thickened left ventricle. Normal splitting of S_2 is present in mild to moderate obstruction. In patients with severe obstruction, the intensity of the aortic component of S_2 is diminished, and S_2 may be split paradoxically (becoming wider in expiration). A fourth heart sound (S_4) may be audible as a result of decreased LV compliance.

The intensity, pitch, and duration of the systolic ejection murmur are other indications of severity. The louder, harsher (higher pitch), and longer the murmur, the greater the degree of obstruction. The murmur will also peak later in systole with increase severity. The typical murmur is audible maximally at the right upper sternal border and radiates to the neck and the left midsternal border. It is usually accompanied by a thrill in the suprasternal notch and, in older patients, over the carotids. In patients with subvalvular aortic stenosis, the murmur may be maximal along the left sternal border or even at the apex. A soft, decrescendo diastolic murmur is present in patients who also have aortic insufficiency, not uncommon with a bicuspid aortic valve or in patients who have had surgery or balloon valvuloplasty. Occasionally, an apical short mid-diastolic rumbling murmur is audible; this murmur should raise suspicion of associated mitral valve stenosis. Careful attention to both upper- and lower-extremity peripheral pulses is essential. Patients with mild aortic stenosis will have normal pulses; as the severity increases, the pulses will become more diminished. Discrepancy between upper- and lower-extremity pulses or a delay in femoral pulses (radio-femoral delay) suggests associated coarctation of the aorta. Discrepancy between the right and left arm pulses in the presence of normal femoral pulses is a sign of possible supravalvar aortic stenosis.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis can usually be made on the basis of the physical examination, and the severity of obstruction confirmed by laboratory tests. If the pressure gradient across the aortic valve is mild, the ECG is likely to be normal. The ECG may occasionally be normal even with mild to moderate obstruction, but evidence of left ventricular hypertrophy (LVH) and LV strain (inverted T waves in left precordial leads) is generally present if moderate to severe stenosis is long-standing. The chest radiograph frequently shows a prominent ascending aorta. Heart size is typically normal or slightly increased. Valvular calcification is noted only in older children and adults. Echocardiography identifies both the site and the severity of the obstruction. Two-dimensional imaging shows LVH and the thickened and abnormally moving aortic valve (Fig. 476.6). The echocardiogram will also demonstrate the number of valve leaflets and their morphology, which leaflets are fused, and the presence of a subaortic membrane or supravalvar stenosis. Associated anomalies of the mitral valve or aortic arch (coarctation of the aorta) or a VSD or PDA are present in up to 20% of cases. In the absence of LV failure, the shortening fraction of the left ventricle may be increased because the ventricle is hypercontractile. In infants with critical aortic

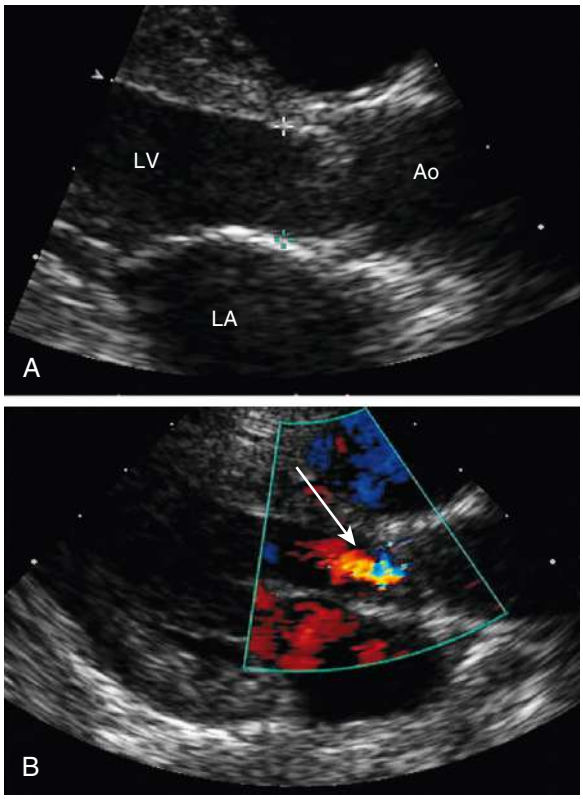

Fig. 476.6 Echocardiogram showing valvar aortic stenosis with regurgitation. **A,** In this parasternal long-axis view, the stenotic aortic valve can be seen doming in systole. The *crosshatch* marks delineate the aortic annulus. **B,** Doppler study shows the presence of aortic regurgitation *(arrow)*. Ao, Aorta; LA, left atrium; LV, left ventricle.

stenosis, the LV shortening fraction is often decreased and may be quite poor. The endocardium may appear bright, indicative of the development of endocardial fibrous scarring, known as **endocardial fibroelastosis**. Doppler studies show the specific site of obstruction and determine the peak and mean systolic LVOT gradients. When severe aortic obstruction is associated with LV dysfunction, the Doppler-derived valve gradient may greatly underestimate the severity of the obstruction because of the low cardiac output across the valve.

Cardiac catheterization is usually not required for diagnostic purposes, but it is usually performed in conjunction with aortic balloon valvuloplasty. Left heart catheterization demonstrates the magnitude of the pressure gradient from the left ventricle to the aorta. The aortic pressure curve is abnormal if the obstruction is severe. In patients with severe obstruction and decreased LV compliance, left atrial pressure is increased and pulmonary hypertension may be present. When a critically ill infant with LVOT obstruction undergoes cardiac catheterization, LV function is often greatly decreased. As with the echocardiogram, the gradient measured across the stenotic aortic valve may underestimate the degree of obstruction because of low cardiac output. Measurement of cardiac output by thermodilution and calculation of the aortic valve area may be helpful.

TREATMENT

Balloon valvuloplasty is indicated for children with moderate to severe valvular aortic stenosis to prevent progressive LV dysfunction and the risk of syncope and sudden death. Valvuloplasty should be advised when the catheter-derived peak-to-peak systolic gradient between the left ventricle and aorta exceeds 60-70 mm Hg at rest, assuming normal cardiac output, or for lesser gradients when symptoms or electrocardiographic changes are present. For more rapidly progressive subaortic obstructive lesions, a gradient of 40-50 mm Hg or the presence of aortic insufficiency is considered an indication for surgery. Balloon valvuloplasty is the procedure of choice even in the neonatal period. Surgical treatment is usually reserved for extremely dysplastic aortic valves that are not amenable to balloon therapy or in patients who also have subvalvar or *supravalvar* aortic stenosis.

Discrete subaortic stenosis can be surgically resected without damage to the aortic valve, the anterior leaflet of the mitral valve, or the conduction system. This type of obstruction is not usually amenable to catheter treatment. Relief of supravalvular stenosis is also achieved surgically, and the results are excellent if the area of obstruction is discrete and not associated with a hypoplastic aorta. In association with supravalvular aortic stenosis, one or both coronary arteries may be stenotic at their origins because of a thick supraaortic fibrous ridge. For patients who have aortic stenosis in association with severe tunnel-like subaortic obstruction, the LVOT can be enlarged by "borrowing" space anteriorly from the right ventricular outflow tract (RVOT) (the **Konno procedure**).

Regardless of whether surgical or catheter treatment has been carried out, aortic insufficiency or calcification with restenosis is likely to occur years or even decades later and eventually require reoperation and often aortic valve replacement. Thus these patients require regular follow-up with a cardiologist. When recurrence develops, it may not be associated with early symptoms. Signs of recurrent stenosis include electrocardiographic signs of LVH, an increase in the Doppler echocardiographic gradient, deterioration in echocardiographic indices of LV function, and recurrence of signs or symptoms during graded treadmill exercise. Evidence of significant aortic regurgitation includes symptoms of heart failure, cardiac enlargement on radiograph, and LV dilation on echocardiogram. The choice of reparative procedure depends on the relative degree of stenosis and regurgitation.

When **aortic valve replacement** is necessary, the choice of procedure often depends on the age of the patient. Homograft valves tend to calcify more rapidly in younger children, but they do not require chronic anticoagulation. Mechanical prosthetic valves are much longer lasting but require anticoagulation, which can be difficult to manage in young children, and they are not available in sizes appropriate for the youngest patients. In adolescent females who are nearing childbearing age, consideration of the teratogenic effects of anticoagulants may warrant the use of a homograft valve. None of these options is perfect for a younger child who requires valve replacement because neither homograft nor mechanical valves grow with the patient. An alternative operation is **aortopulmonary translocation (Ross procedure)**; it involves removing the patient's own pulmonary valve and using it to replace the abnormal aortic valve. A homograft is then placed in the pulmonary position. The potential advantage of this procedure is the possibility for growth of the translocated living "neoaortic" valve and the increased longevity of the homograft valve when placed in the lower-pressure pulmonary circulation. The long-term success of this operation, especially in young children, is still being investigated.

Transcatheter aortic valve replacement (or implantation) (TAVR) uses porcine or bovine (Melody or Sapien) valve tissue sewn into a self-expanding frame. These devices can be implanted in the cardiac catheterization laboratory using a femoral or carotid approach, or transapically through the chest wall, or in a hybrid procedure after a surgical thoracotomy. Initially used mainly in adults who were too ill to be candidates for standard surgical replacement, TAVR is gaining acceptance for carefully selected children who are not good surgical candidates. Short-term outcomes are equivalent to surgical valve replacement. Long-term complications include possible valve regurgitation or perivalvular leaks.

PROGNOSIS

Neonates with critical aortic stenosis may have severe heart failure and deteriorate rapidly to a low-output shock state. Emergency surgery or balloon valvuloplasty is lifesaving, but the mortality risk is not trivial. Neonates who die of critical aortic stenosis frequently have significant LV endocardial fibroelastosis. Those who survive may develop signs of LV diastolic dysfunction (restrictive cardiomyopathy) and eventually require cardiac transplantation (see Chapter 492).

In older infants and children with mild to moderate aortic stenosis, the prognosis is reasonably good, although disease progression over

5-10 years is common. Patients with aortic valve gradients <40-50 mm Hg are considered to have *mild* disease; those with gradients of 40-70 mm Hg have *moderate* disease. These patients usually respond well to treatment (either surgery or valvuloplasty), although reoperations on the aortic valve are often required later in childhood or in adult life, and many patients eventually require valve replacement. In unoperated patients with severe obstruction, sudden death is a significant risk and often occurs during or immediately after exercise. Subaortic stenosis secondary to hypertrophic cardiomyopathy is one of the causes of sudden cardiac death in adolescents and young adults.

Patients with moderate to severe degrees of aortic stenosis should not participate in active competitive sports. In those with milder disease, sports participation is less severely restricted. The status of each patient should be reviewed at least annually and intervention advised if progression of signs or symptoms occurs. Prophylaxis against infective endocarditis is no longer recommended unless a prosthetic or transcatheter (TAVR) valve has been inserted.

Older children and adults with isolated bicuspid aortic valve are at increased risk for developing dilation of their ascending aorta, even in the absence of significant stenosis. This risk increases with age, and the rate of increase is greatest in those with the largest aortic roots. In children, this dilation is usually mild and remains stable over many years of observation, but in young adults and older patients, the aorta can dilate substantially and progressively. Whether these patients have some undiagnosed form of connective tissue disorder remains to be determined (this form of dilation is similar to that seen in Marfan syndrome). Patients with Turner syndrome and bicuspid aortic valve also have an increased risk of aortic dilation. Although dissection and rupture are described complications of severe aortic root dilation in adults, there are not yet sufficient data to determine these risks in children, and careful monitoring with echocardiogram, CT, or MRI is warranted.

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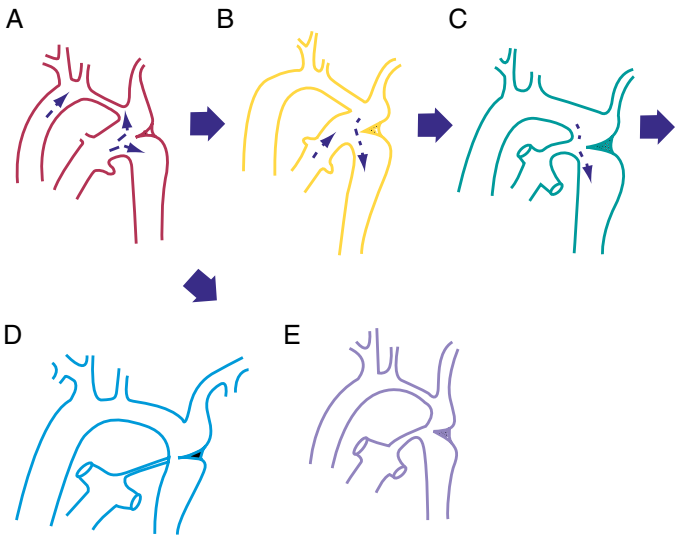

Fig. 476.7 Metamorphosis of coarctation. **A,** Fetal prototype with no flow obstruction. **B,** Late gestation. The aortic ventricle increases its output and dilates the hypoplastic segment. Antegrade aortic flow bypasses the shelf via the ductal orifice. **C,** Neonate. Ductal constriction initiates the obstruction by removing the bypass and increasing antegrade arch flow. **D,** Mature juxtaductal stenosis. The bypass is completely obliterated, and intimal hypoplasia on the edge of the shelf is aggravating the stenosis. Collaterals develop. **E,** Persistence of the infantile-type fetal prototype. An intracardiac left-sided heart obstruction precludes an increase in antegrade aortic flow before or after birth. Both isthmus hypoplasia and a contraductal shelf are present. Lower-body flow often depends on the patency of the ductus. *(From Gersony WM. Coarctation of the aorta. In: Adams FH, Emmanouilides GC, Riemenshneider T, eds. Moss Heart Disease in Infants, Children, and Adolescents, 4th ed. Baltimore: Williams & Wilkins; 1989.)*

476.6 Coarctation of the Aorta

Daniel Bernstein

Constrictions of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus **(juxtaductal coarctation)**. The anomaly is responsible for 5–8% of congenital heart disease and occurs twice as often in males as in females. Coarctation of the aorta is associated with a bicuspid aortic valve in >70% of patients; mitral valve abnormalities (a supravalvular mitral ring or parachute mitral valve) and subaortic stenosis are other associated lesions. When this group of left-sided obstructive lesions occurs together, they are referred to as **Shone complex**. Coarctation of the aorta is found in up to 20% of patients with **Turner syndrome** (see Chapters 99.4 and 626.1); ~5–12% of females with coarctation have Turner syndrome.

PATHOPHYSIOLOGY

Coarctation of the aorta can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (previously referred to as *preductal* or *infantile-type coarctation;* Fig. 476.7). Often, both components are present. It is postulated that coarctation may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD). Alternatively, it has been theorized that coarctation may be caused by abnormal extension of contractile ductal tissue into the aortic wall.

In patients with discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although LV hypertension and hypertrophy result. In the first few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in these acyanotic infants. With more severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, RV blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on RV output. In this situation the femoral pulses are palpable, and differential blood pressures may not be helpful in making the diagnosis. However, the ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being well oxygenated and the lower extremities cyanotic. This is one of the main reasons for performing upper- and lower-limb oxygen saturation screening in the newborn because subtle differences in saturation may not be discernable visually. Such infants may have severe pulmonary hypertension and high pulmonary vascular resistance. Signs of heart failure are prominent. Occasionally, severely hypoplastic segments of the aortic isthmus may become completely atretic and result in an interrupted aortic arch, with the left subclavian artery arising either proximal or distal to the interruption.

Blood pressure (BP) is elevated in the vessels that arise proximal to the coarctation; BP and pulse pressure are lower below the constriction. The hypertension is not caused by the mechanical obstruction alone, but also involves neurohumoral mechanisms. Unless surgically corrected in infancy, coarctation of the aorta usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation may become greatly enlarged and tortuous by early adulthood.

CLINICAL MANIFESTATIONS

Coarctation of the aorta recognized after infancy may not be associated with significant symptoms, although these may be revealed on closer questioning. Some children or adolescents complain about weakness or pain/claudication (or both) in the legs after exercise, but in many cases, even patients with severe coarctation are asymptomatic. Older

children are frequently brought to the cardiologist's attention when they are found to be hypertensive on routine physical examination.

The classic sign of coarctation of the aorta is a disparity in pulsation and BP in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40% of patients), in contrast to bounding pulses palpated in the arms and carotid vessels. However, in patients with large numbers of collaterals, the pulse and BP may not be much diminished in the lower extremities; in these cases, diagnosis depends on palpation of the radial and femoral pulses simultaneously for the presence of a **radial-femoral delay**. Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons *(except neonates),* systolic BP in the legs obtained by the cuff method is usually 10-20 mm Hg higher than that in the arms. In coarctation of the aorta, BP in the legs is lower than that in the arms; frequently, it is difficult to obtain. This differential in BPs is common in patients with coarctation who are older than 1 year, approximately 90% of whom have systolic hypertension in an upper extremity >95th percentile for age. It is important to determine the BP in each arm; a BP higher in the right than the left arm suggests involvement of the left subclavian artery in the area of coarctation. Occasionally, the right subclavian may arise anomalously from below the area of coarctation and result in a left arm BP that is higher than the right. With exercise, a more prominent rise in upper arm BP occurs, and the upper- to lower-extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70% of cases). A short systolic murmur is often heard along the left sternal border at the third and fourth intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. With a bicuspid aortic valve, the typical murmur of aortic stenosis can be heard at the upper right and mid-left sternal borders. Occasionally, more significant degrees of obstruction are noted across the aortic valve. The presence of a low-pitched mid-diastolic murmur at the apex suggests mitral valve stenosis. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly. In these patients, a palpable thrill can sometimes be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe coarctation, usually including some degree of transverse arch hypoplasia, initially have signs of lower-body hypoperfusion, acidosis, and severe heart failure. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit **differential cyanosis**, best demonstrated by simultaneous oximetry of the upper and lower extremities. On physical examination the heart is large, and a systolic murmur is heard along the left sternal border.

Diagnosis

Findings on chest x-ray examination depend on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe coarctation. In patients with less severe forms of coarctation, the findings may not be that striking until after the first decade, when the heart tends to be mildly or moderately enlarged because of LV prominence. The enlarged left subclavian artery typically produces a prominent shadow in the left superior mediastinum. **Notching of the inferior border of the ribs** from pressure erosion by enlarged collateral vessels is common by late childhood. In most patients the descending aorta has an area of poststenotic dilation.

The ECG is usually normal in young children with milder degrees of coarctation but demonstrates LV hypertrophy in older patients. Neonates and young infants display right or biventricular hypertrophy. The segment of coarctation can generally be visualized by 2D echocardiography (Fig. 476.8); associated anomalies of the mitral and aortic valve can also be demonstrated. The descending aorta is hypopulsatile, and color Doppler demonstrates the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of coarctation; in the presence of a PDA, however, the severity of the narrowing may be underestimated. CT and MRI

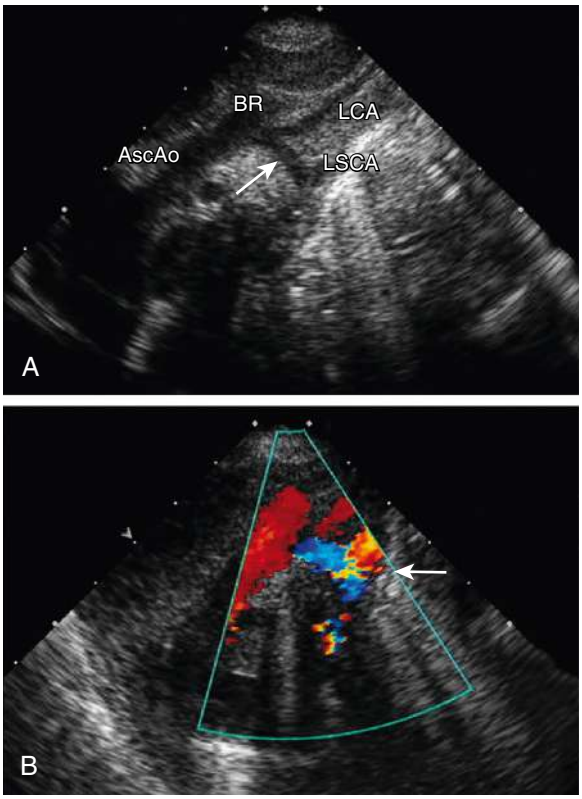

Fig. 476.8 Echocardiogram demonstrating coarctation of the aorta with hypoplastic transverse arch. **A,** Suprasternal notch 2D echocardiogram showing marked narrowing beginning just distal to the brachiocephalic artery. **B,** Color Doppler demonstrates turbulent flow in the juxtaductal area *(arrow).* AscAo, Ascending aorta; BR, brachiocephalic artery; LCA, left carotid artery; LSCA, left subclavian artery.

are valuable noninvasive tools for evaluation of coarctation when the echocardiogram is equivocal (Fig. 476.9). Cardiac catheterization with selective left ventriculography and aortography is useful in occasional patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by echocardiography, CT, or MRI, diagnostic catheterization is not usually required before surgery.

TREATMENT

In **neonates** with severe coarctation of the aorta, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of prostaglandin E_1 to reopen the ductus and reestablish adequate lower-extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. **Older infants** with heart failure but good perfusion should be managed with anticongestive measures to improve their clinical status in preparation for surgical intervention. There is usually no reason to delay surgical repair waiting for patient growth; successful repairs have been performed even in small premature infants.

Older children with significant coarctation of the aorta should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the second decade of life, when there may be decreased LV function and degenerative changes in the aortic wall. For patients with significant left ventricular dysfunction, relief of the obstruction can improve function as afterload on the ventricle is dramatically decreased; however, if fibrosis has occurred, patients can have residual left ventricular dysfunction. If cardiac function is normal, satisfactory repair and long-term outcome are possible well into mid-adult life.

Surgery remains the treatment of choice for isolated juxtaductal coarctation of the aorta in neonates, infants, and young children at most centers; several surgical techniques are used. The area of coarctation can be excised and a primary reanastomosis performed. Most often, the transverse aorta is opened and an "extended end-to-end" anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian

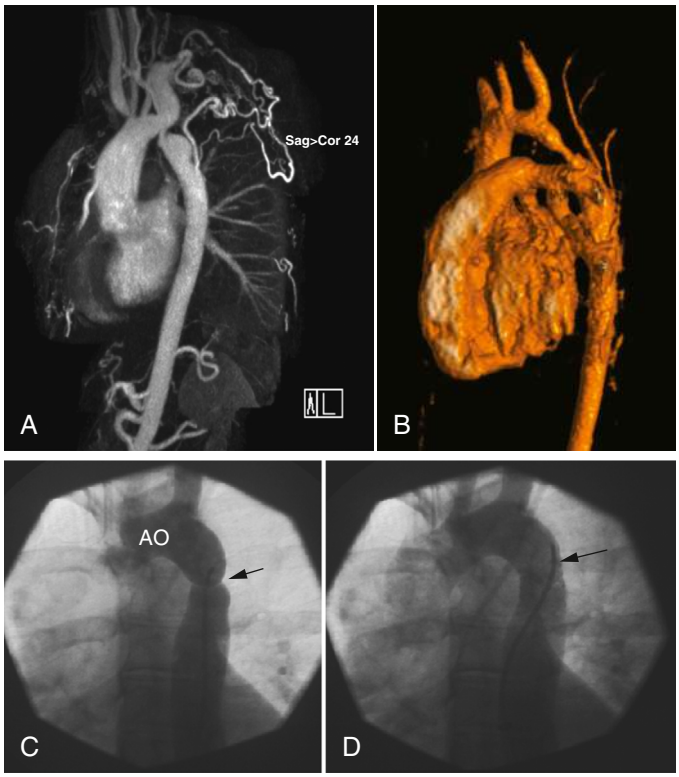

Fig. 476.9 Coarctation of the aorta. A, CT angiogram of coarctation. B, 3D reconstruction. Angiograms of the coarctation before (C) and after (D) stenting *(arrows)*. AO, Aorta. *(Adapted from Webb GD, Smallhorn JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75.41, p. 1561.)*

flap procedure, which involves division of the left subclavian artery and its incorporation into the wall of the repaired coarctation, has fallen out of favor because of a higher degree of residual stenosis. Some centers favor a patch aortoplasty, in which the area of coarctation is enlarged with a roof of prosthetic material. The use of **primary angioplasty** for native coarctation has been effective in older children and adults. In infants ≥3 months of age, balloon angioplasty has been as effective as surgery but is associated with higher rates of recoarctation requiring intervention (repeat angioplasty or surgery) and aortic aneurysm formation. Surgery is the treatment of choice for the symptomatic neonate. Angioplasty is the treatment of choice for recoarctation. **Primary stent placement** in the catheterization laboratory is considered in older children, where the stent can be expanded if needed to keep up with patient growth and for young adults (see Fig. 476.9). For patients who present with severe LV dysfunction, where surgical intervention may be associated with increased risk, catheter-based treatments are often considered.

After surgery, a striking increase in the amplitude of the pulse in the lower extremities is noted. In the immediate postoperative course, *rebound hypertension* can occur and requires medical management. This exaggerated acute hypertension gradually subsides, and in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may result from associated cardiac anomalies, a residual flow disturbance across the repaired area, or collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping (if collaterals are poorly developed), chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap approach is used, the radial pulse and BP in the left arm are diminished or absent.

POSTCOARCTECTOMY SYNDROME

Postoperative **mesenteric arteritis** may be associated with acute hypertension and abdominal pain in the immediate postoperative period. The pain varies in severity and may occur in conjunction with anorexia, nausea, vomiting, leukocytosis, intestinal hemorrhage, bowel necrosis, and small bowel obstruction. Relief is usually obtained with antihypertensive drugs (e.g., nitroprusside, esmolol, captopril) and intestinal decompression; surgical exploration is rarely required for bowel obstruction or infarction.

PROGNOSIS

Although restenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 year of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and for aortic aneurysm at the anastomotic site. Should recoarctation occur, **balloon angioplasty** is the procedure of choice. In these patients, scar tissue from a previous surgery may make reoperation more difficult, yet it makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. **Intravascular stents** are typically used, especially in adolescents and young adults, with generally excellent results.

Repair of coarctation in the second decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of **adult-type chronic hypertension** may occur, even in patients with adequately resected coarctation.

Abnormalities of the aortic valve are present in a majority of patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA with coarctation of the aorta is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also occasionally seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with defective elastic and medial tissue, or rupture of normal vessels; these events are secondary to hypertension. Children with **PHACE syndrome** (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies syndrome) may have strokes (see Table 691.5). Abnormalities of the subclavian arteries may include involvement of the left subclavian artery in the area of coarctation, stenosis of the orifice of the left subclavian artery, and anomalous origin of the right subclavian artery.

Untreated, the great majority of older patients with coarctation of the aorta would succumb between ages 20 and 40 years; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, heart failure, hypertensive encephalopathy, or intracranial hemorrhage. Heart failure may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant complication in these adult patients. Aneurysms of the descending aorta or the enlarged collateral vessels may develop.

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476.7 Coarctation with Ventricular Septal Defect

Daniel Bernstein

In most cases, coarctation is the major anomaly causing the severe symptoms, and resection of the coarcted segment results in striking improvement. Repair of both the VSD and coarctation is usually performed at the same operation through a midline sternotomy using cardiopulmonary bypass.

476.8 Coarctation with Other Cardiac Anomalies and Interrupted Aortic Arch

Daniel Bernstein

Coarctation often occurs in infancy in association with other major cardiovascular anomalies, including hypoplastic left heart, severe mitral or aortic valve disease, transposition of the great arteries, and variations of

double-outlet or single-ventricle. The clinical manifestations depend on the effects of the associated malformations and on the coarctation itself.

Coarctation of the aorta associated with severe **mitral** and **aortic valve disease** may have to be treated within the context of hypoplastic left heart syndrome (see Chapter 480.10), even if the LV chamber is not severely hypoplastic. Such patients usually have a long segment of narrow, transverse aortic arch in addition to an isolated coarctation at the site of the ductus arteriosus. Coarctation of the aorta with **transposition of the great arteries** or **single ventricle** may be repaired alone or in combination with other corrective or palliative measures.

Complete interruption of the aortic arch is the most severe form of coarctation and is usually associated with other intracardiac pathology. Interruption may occur at any level, although it is most often seen between the left subclavian artery and the insertion of the ductus arteriosus **(type A)**, followed in frequency by those between the left subclavian and left carotid arteries **(type B)**, or between the left carotid and brachiocephalic arteries **(type C)**. In newborns with an interrupted aortic arch, the ductus arteriosus provides the sole source of blood flow to the descending aorta, and differential oxygen saturations between the right arm (normal saturation) and the legs (decreased saturation) is noted. When the ductus begins to close, severe congestive heart failure, lower-extremity hypoperfusion, and anuria usually develop, progressing to shock. Patients with an interrupted aortic arch can be supported with prostaglandin E_1 to keep the ductus open before surgical repair. As one of the **conotruncal malformations**, an interrupted aortic arch, especially type B, can be associated with **DiGeorge syndrome** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletion of a segment of chromosome 22q11, known as the **DiGeorge critical region**.

476.9 Congenital Mitral Stenosis

Daniel Bernstein

Congenital mitral stenosis is a rare anomaly that can be either isolated or associated with other defects, the most common being subvalvar and valvar aortic stenosis and coarctation of the aorta **(Shone complex)**. The mitral valve may be funnel shaped, with thickened leaflets and chordae tendineae that are shortened and deformed. Other mitral valve anomalies associated with stenosis include **parachute** mitral valve, caused by a single papillary muscle, and **double-orifice** mitral valve.

If the stenosis is moderate to severe, symptoms usually appear within the first 2 years of life. These infants have failure to thrive and various degrees of dyspnea and pallor. In some patients, wheezing may be a dominant symptom, and a misdiagnosis of bronchiolitis or reactive airway disease may have been made. Heart enlargement because of dilation and hypertrophy of the right ventricle and left atrium is common. Most patients have rumbling apical diastolic murmurs, but because the pressure gradients in diastole are not very high, the auscultatory findings may be relatively obscure. S_2 is split with a loud P_2 if pulmonary hypertension is present. An opening snap of the mitral valve may be present. The ECG reveals RVH and may show bifid or spiked P waves indicative of left atrial enlargement. Radiographs usually show left atrial and RV enlargement and pulmonary congestion in a perihilar or venous pattern. The echocardiogram is diagnostic and shows thickened mitral valve leaflets, a significant reduction of the mitral valve orifice, abnormal papillary muscle structure (or a single papillary muscle), and an enlarged left atrium with a normal or small left ventricle. A **double-orifice mitral valve** is one variant that can usually be seen on echocardiogram. Doppler studies demonstrate a mean pressure gradient across the mitral orifice during diastole. Associated anomalies such as aortic stenosis and coarctation can be evaluated. Cardiac catheterization is often performed to confirm the transmitral pressure gradient before surgery. An increase in RV, pulmonary artery, and pulmonary capillary wedge pressure can be noted. Angiocardiography shows delayed emptying of the left atrium and the small mitral orifice.

The results of surgical treatment depend on the anatomy of the valve, but if the mitral orifice is significantly hypoplastic, reduction of the gradient may be difficult. In some patients, a mitral valve prosthesis is required, and if the valve orifice is too small, the prosthesis may be placed in the supramitral position. However, whatever prosthesis is used, it must be replaced serially as the child grows. These patients must be anticoagulated, usually with warfarin, and although manageable in older children, complications of excessive and insufficient anticoagulation are more common in infancy. Transcatheter balloon valvuloplasty has been used as a palliative procedure with mixed results, except in the situation of rheumatic mitral stenosis. Recent experience using the percutaneous Melody stent-valve in selected patients in the mitral position is encouraging.

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476.10 Pulmonary Venous Hypertension

Daniel Bernstein

A variety of lesions may give rise to chronic pulmonary venous hypertension, which, when extreme, may result in pulmonary arterial hypertension and right-sided heart failure. These lesions include congenital **mitral stenosis**, **mitral insufficiency**, **total anomalous pulmonary venous return with obstruction**, **left atrial myxomas**, **cor triatriatum**, individual **pulmonary vein stenosis**, and **supravalvular mitral rings**. Early symptoms can be confused with chronic pulmonary disease such as asthma because of a lack of specific cardiac findings on physical examination. Subtle signs of pulmonary hypertension may be present. The ECG shows RVH with spiked P waves. Radiographic studies demonstrate prominence of the pulmonary veins in the hilar region and enlargement of the right ventricle and atrium and the main pulmonary artery; the left atrium is normal in size or only slightly enlarged.

The echocardiogram may demonstrate left atrial myxoma, cor triatriatum, stenosis of one or more pulmonary veins, or a mitral valve abnormality (e.g., supravalvar mitral ring). Cardiac catheterization excludes the presence of a shunt and demonstrates pulmonary hypertension with elevated pulmonary arterial wedge pressure. Left atrial pressure is normal if the lesion is at the level of the pulmonary veins, but it is elevated if the lesion is at the level of the mitral valve. Selective pulmonary arteriography usually delineates the anatomic lesion. Cor triatriatum, left atrial myxoma, and supravalvular mitral rings can all be successfully managed surgically.

The differential diagnosis includes **pulmonary venoocclusive disease**, an idiopathic process that produces obstructive lesions in one or more pulmonary veins. The cause is uncertain, and disease that begins in one vein can spread to others. Although it is usually encountered in patients after repair of obstructed total anomalous pulmonary venous return (see Chapter 480.7), it can occur sporadically or in families in the absence of congenital heart disease. Pathogenic variants in *BMPR2* may be seen in the familial or sporadic cases. The patient initially presents with symptoms similar to left-sided heart failure on the basis of congested lungs with apparent pulmonary edema. Dyspnea, fatigue, and pleural effusions are common. Left atrial pressure is normal, but pulmonary arterial wedge pressure is usually elevated. A normal wedge pressure may be encountered if collaterals have formed, or the wedge recording is performed in an uninvolved segment. Angiographically, the pulmonary veins return normally to the left atrium, but one or more pulmonary veins are narrowed, either focally or diffusely. Sporadic or familial cases present with a primary pulmonary hypertension phenotype, with dyspnea and cyanosis. However, treatment with a primary pulmonary hypertension regimen will precipitate pulmonary edema.

Studies using lung biopsy have demonstrated pulmonary venous and, occasionally, arterial involvement. Pulmonary veins and venules demonstrate fibrous narrowing or occlusion, and pulmonary artery thrombi may be present. Attempts at surgical repair, balloon dilation, and transcatheter stenting have not significantly improved the generally poor prognosis of these patients. Use of antiproliferative agents with imatinib with or without bevacizumab has demonstrated success in preliminary studies. Combined heart-lung transplantation is often the only alternative therapeutic option (see Chapter 492.2).

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Chapter 477

Acyanotic Congenital Heart Disease: Regurgitant Lesions

477.1 Pulmonary Valvular Insufficiency and Congenital Absence of the Pulmonary Valve

Daniel Bernstein

Pulmonary valvular insufficiency most often accompanies other cardiovascular diseases (surgical repair of pulmonary valve stenosis) or may be secondary to severe **pulmonary hypertension**. Some degree of incompetence of the valve is an expected result after surgery for right ventricular outflow tract (RVOT) obstruction, including pulmonary valvotomy in patients with **valvular pulmonic stenosis** or valvotomy with infundibular resection in patients with **tetralogy of Fallot**. Isolated congenital insufficiency of the pulmonary valve is rare, and these patients are usually asymptomatic because the insufficiency is generally mild.

The prominent physical sign is a decrescendo diastolic murmur at the upper and mid-left sternal border, which has a lower pitch than the murmur of aortic insufficiency because of the lower pressure involved. Radiographs of the chest show prominence of the main pulmonary artery and, if the insufficiency is severe, right ventricular (RV) enlargement. The electrocardiogram (ECG) is normal or shows an rSR′ pattern in the right precordial leads (V_1, V_2) and minimal or no RV hypertrophy. Pulsed and color Doppler studies demonstrate retrograde flow from the pulmonary artery into the right ventricle during diastole. Echocardiography can give qualitative measures of RV volume; cardiac magnetic resonance angiography (MRA) is the best method for quantifying RV volume, the regurgitant fraction, and RV systolic function (ejection fraction). Mild pulmonary valvular insufficiency is generally well tolerated and does not require surgical treatment. When pulmonary insufficiency is moderate to severe and the right ventricle becomes significantly dilated and/or if tricuspid insufficiency has begun to develop, re-repair, replacement with a homograft valve, or transcatheter stent-valve placement may become necessary to preserve RV function.

Congenital absence of the pulmonary valve is usually associated with a ventricular septal defect (VSD), often in the context of tetralogy of Fallot (see Chapter 479.1). In many of these neonates, the pulmonary arteries become widely dilated and compress the bronchi, resulting in recurrent episodes of wheezing, pulmonary collapse, and pneumonitis. The presence and degree of cyanosis are variable. Florid pulmonary valvular incompetence may not be well tolerated, and death may occur from a combination of bronchial compression, hypoxemia, and heart failure. Correction involves plication of the massively dilated pulmonary arteries, closure of the VSD, and placement of a homograft across the RVOT.

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477.2 Congenital Mitral Insufficiency

Daniel Bernstein

Congenital mitral insufficiency is rare as an isolated lesion and is more often associated with other anomalies. It is most frequently encountered in combination with an **atrioventricular septal defect**, either an ostium primum defect or a complete atrioventricular septal defect (see Chapter 475.5) where the insufficient jet is through a cleft in the mitral valve. Mitral insufficiency is also seen in patients with dilated cardiomyopathy (see Chapter 488.1) when the left ventricular (LV) function deteriorates, the chamber dilates, and the valve ring is stretched. In adults, mitral insufficiency can be the result of ischemic injury to a papillary muscle; this is uncommon in children. Mitral insufficiency may also be encountered in conjunction with coarctation of the aorta, VSD, corrected transposition of the great vessels, anomalous origin of the left coronary artery from the pulmonary artery, or Marfan syndrome. In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated mitral insufficiency.

In mitral insufficiency caused by a congenitally malformed valve, the mitral valve annulus may be dilated, the chordae tendineae short and may insert anomalously, and the valve leaflets are deformed. When mitral insufficiency is severe enough to cause clinical symptoms, the left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes dilated and mildly hypertrophied. Pulmonary venous pressure is increased, and the increased pressure can ultimately result in pulmonary hypertension and RV hypertrophy and dilation. Mild lesions produce no symptoms; the only abnormal sign is an apical holosystolic murmur of mitral regurgitation. In contrast, moderate to severe regurgitation results in symptoms that can appear at any age, including poor growth, frequent respiratory infections, fatigue on exertion, and episodes of pulmonary edema or congestive heart failure. Often, a diagnosis of reactive airways disease will have been made because of the similarity in pulmonary symptoms, including wheezing, which may be a dominant finding in infants and young children. The presence of a murmur helps distinguish these two etiologies.

The typical murmur of mitral insufficiency is a moderately high-pitched, apical blowing, holosystolic murmur. The murmur radiates from the apex toward the mid-left sternal border. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve (physiologic mitral stenosis). The pulmonic component of the second heart sound will be accentuated if there is pulmonary hypertension. The ECG usually shows bifid P waves consistent with left atrial enlargement, signs of LV hypertrophy, and sometimes signs of RV hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times can be massive. The left ventricle is also enlarged and pulmonary vascularity prominent, especially in the perihilar areas. The echocardiogram demonstrates the enlarged left atrium and left ventricle and defines the structure of the valve, the presence or absence of a cleft, and the chordal apparatus. 3D echocardiography is especially useful for this imaging. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure and left ventricular end-diastolic pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography demonstrates the severity of mitral regurgitation.

Surgical **mitral valvuloplasty** can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified, as they will need to be addressed at the time of valve repair. If the valve requires replacement, several alternatives are available, including mechanical (used mainly for older children) and bioprosthetic, as well as the use of the Melody stent-valve. These can be inserted during a **hybrid procedure** (surgery and catheterization). A cardiac catheter laboratory–inserted device (MitraClip), used mostly in adults, has been used in a few selected pediatric patients to cinch together the anterior and posterior mitral valve leaflets, reducing insufficiency by creating a double-orifice mitral valve.

477.3 Mitral Valve Prolapse

Daniel Bernstein

Mitral valve prolapse (MVP) results from an abnormal mitral valve mechanism that causes billowing of one or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of ventricular systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Primary mitral valve prolapse is common, is present in 2–3% of the population, is more common in females, and may be sporadic or inherited as an autosomal dominant trait (less often X-linked) with variable expression. Pathogenic variants in *DCHS1, LMCD1, TNS1,* and *DZIP1* are possible genes associated with nonsyndromic MVP. It is a common finding in patients with Marfan syndrome, Loeys-Dietz syndrome, mitral-aortic-skeleton-skin (MASS) phenotype, familial myxomatous valvular degeneration, fragile X syndrome, mucopolysaccharidoses, Stickler syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum and can also be associated with hyperthyroidism. Fibromyxomatous degeneration of the valve leaflets causes them to be thickened and elongated.

The abnormal signs are auscultatory, although occasional patients may have chest pain and/or palpitations. The apical murmur is late systolic and may be preceded by a click, but these signs may vary in the same patient, and at times, only the click is audible. Sudden standing, or the strain phase of the Valsalva maneuver, decreases LV volume, so the click moves closer to S_1 and the murmur becomes longer. Squatting (or the release phase of the Valsalva maneuver) increases LV volume, so that the click moves away from S_1 and the murmur is shortened. Arrhythmias may occur, primarily unifocal or multifocal premature ventricular contractions. In young adults, MVP has been associated with sudden cardiac death secondary to ventricular arrhythmias.

The ECG is usually normal but may show biphasic T waves, especially in leads II, III, aVF, and V_6; the T-wave abnormalities may vary at different times in the same patient. The chest radiograph is normal. The echocardiogram shows a characteristic posterior movement of the posterior mitral leaflet during mid- or late ventricular systole or demonstrates pansystolic prolapse of both the anterior and posterior mitral leaflets. These echocardiographic findings must be interpreted cautiously because the appearance of minimal mitral prolapse may be a normal variant. Prolapse is more precisely defined by single or bileaflet prolapse of >2 mm beyond the long-axis annular plane of the valve with or without leaflet thickening. Prolapse with valve thickening >5 mm is "classic"; a lesser degree is "nonclassic." Two-dimensional echocardiography shows that both the free edge and the body of the mitral leaflets move posteriorly in systole toward the left atrium. Doppler is then used to assess the presence and severity of mitral regurgitation.

This lesion is not progressive in childhood, and specific therapy is not indicated. Antibiotic prophylaxis is not recommended during surgery and dental procedures (see Chapter 486). This recommendation is controversial because certain features (regurgitation, thickened redundant leaflets) may increase the risk of endocarditis.

Adults (males more often than females) with MVP are at increased risk for cardiovascular complications (sudden death, arrhythmia, cerebrovascular accident, progressive valve dilation, heart failure, and endocarditis) if they have thickened (>5 mm) and redundant mitral valve leaflets. Risk factors for morbidity also include poor LV function, moderate to severe mitral regurgitation, and left atrial enlargement. MVP with severe valve regurgitation, or heart failure, or significant arrhythmias may require initial valve repair or replacement. Beta-blocking agents have been used for patients with palpitations and some arrhythmias. Most patients are asymptomatic and require no treatment.

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477.4 Tricuspid Regurgitation

Daniel Bernstein

Isolated congenital tricuspid regurgitation is most often associated with **Ebstein anomaly of the tricuspid valve** (see Chapter 479.7). Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form or only develop cyanosis with exercise, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis.

In pediatric patients, tricuspid regurgitation is most often associated with congenital heart disease and/or RV dysfunction. When the right ventricle becomes dilated because of volume overload (e.g., pulmonary insufficiency) or intrinsic myocardial disease (dilated cardiomyopathy), the tricuspid annulus also enlarges, with separation of the leaflets and resultant valve insufficiency. This form of regurgitation may improve if the cause of the RV dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation can also be encountered in patients with congenitally corrected transposition of the great arteries (see Chapter 479) and in patients with hypoplastic left heart syndrome after surgical palliation; in both of these situations the RV is pumping at systemic pressure. Isolated tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Lastly, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction, but is also seen as a result of valve injury caused by endomyocardial biopsy.

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Chapter 478

Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 124.

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease (CHD) is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 121.2.

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Daniel Bernstein

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Chapter 478

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CARDIAC DISEASE LEADING TO CYANOSIS

CHD produces cyanosis when obstruction to right ventricular inflow or outflow causes intracardiac right-to-left shunting or when complex anatomic defects cause an admixture of pulmonary (deoxygenated) and systemic (oxygenated) venous return somewhere in the heart. Cyanosis from pulmonary edema may also develop in patients with heart failure caused by left-to-right shunts, although the degree of desaturation is usually less severe. In general, right ventricular outflow obstruction without an intracardiac shunt (e.g., isolated valvar pulmonary stenosis) does not cause cyanosis; however, in the newborn period, cyanosis may be caused by right-to-left shunting across the foramen ovale in the presence of elevated right-sided filling pressures. **Persistent pulmonary hypertension of the newborn (PPHN)** is another cause of right-to-left shunting at the atrial level in the newborn period (see Chapter 130).

DIFFERENTIAL DIAGNOSIS

The **hyperoxia test** is one method of distinguishing cyanotic CHD from pulmonary disease. This test is based on the premise that neonates with cyanotic CHD usually are unable to significantly raise their arterial blood partial pressure of oxygen (Pao_2) during administration of 100% oxygen, whereas in infants with pulmonary disease, high levels of intraalveolar Po_2 will overcome at least some of the ventilation-perfusion abnormalities and reverse the hypoxia. This test is performed using a hood rather than nasal cannula or face mask to guarantee delivery of almost 100% oxygen to the patient. False-positive tests can occur if this is not done correctly. In a healthy newborn, the Pao_2 should rise above 300 mm Hg; if between 150 and 300 mm Hg, noncardiac etiologies (pulmonary disease, central nervous system disorders, methemoglobinemia) are most likely. This is not 100% confirmative, however, because some patients with cyanotic CHD may be able to increase their Pao_2 to >150 mm Hg because of favorable intracardiac streaming patterns. In infants with cyanosis from a central nervous system disorder, the Pao_2 usually normalizes completely during artificial ventilation. If the Pao_2 is between 100 and 150 mmHg, then cyanotic congenital heart lesions, increased pulmonary blood flow (mixing lesions, see Chapter 480), or PPHN are more likely. If the Pao_2 is less than 100 mm Hg, then CHD with decreased pulmonary blood flow (see Chapter 479) is more likely. Another clue to etiology is that hypoxia in many heart lesions is relatively constant, whereas in respiratory disorders and in PPHN, Pao_2 often varies with time or changes in ventilator management. For example, hyperventilation may improve the hypoxia in neonates with PPHN but only occasionally in those with cyanotic CHD.

Although a significant heart murmur usually suggests a cardiac basis for the cyanosis, several of the more severe cardiac defects (e.g., transposition of the great vessels) may not initially be associated with a murmur. The chest radiograph may be helpful in the differentiation of pulmonary and cardiac disease; in the latter, it also indicates whether pulmonary blood flow is increased, normal, or decreased (Fig. 478.1) as well as shows alterations in cardiac size.

Two-dimensional echocardiography with Doppler is the definitive noninvasive test to determine the presence of CHD. With today's high-quality echocardiography, cardiac catheterization is less often used for diagnostic purposes and is usually performed to examine structures that are less well visualized by echocardiography, such as distal branch pulmonary arteries and aortopulmonary collateral arteries in patients with tetralogy of Fallot with pulmonary atresia (see Chapter 479.2) or coronary arteries and right ventricular sinusoids in patients with pulmonary atresia and intact ventricular septum (see Chapter 479.3). If echocardiography is not immediately available to confirm a diagnosis of cyanotic CHD, the clinician caring for a newborn with possible cyanotic CHD should not hesitate to start a prostaglandin infusion (for a possible ductal-dependent lesion). Because of the risk of hypoventilation associated with prostaglandins, a practitioner skilled in neonatal endotracheal intubation must be available.

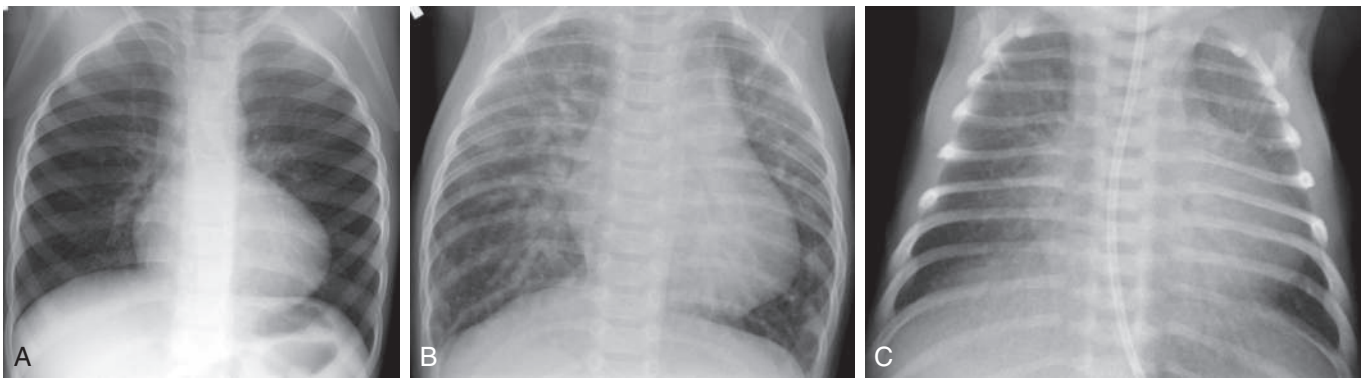

Fig. 478.1 Physiology of congenital heart disease delineated by chest radiography. **A,** Mild cardiomegaly with an upturned cardiac apex, a concave main pulmonary artery segment, and symmetric, severely diminished pulmonary blood flow in a 4-yr-old child with tetralogy of Fallot/pulmonary atresia. **B,** Moderate cardiomegaly and symmetric, increased pulmonary blood flow in a 3-mo-old infant with a large atrial septal defect and ventricular septal defect. **C,** Moderate cardiomegaly with interstitial edema in an 8-day-old newborn with critical aortic stenosis. *(From Frost JL, Krishnamurthy R, Sena L. Cardiac imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology—The Requisites, 4th ed. Philadelphia: Elsevier; 2017: Fig. 3.9, p. 68.)*

Chapter 479

Cyanotic Congenital Heart Disease: Lesions Associated with Decreased Pulmonary Blood Flow

479.1 Tetralogy of Fallot

Daniel Bernstein

Tetralogy of Fallot is one of the **conotruncal** family of heart lesions in which the primary defect is an anterior deviation of the *infundibular septum* (the muscular septum that separates the aortic and pulmonary outflows during division of the truncus arteriosus). The consequences of this deviation are the four components that Fallot initially described: (1) obstruction to right ventricular (RV) outflow (pulmonary stenosis); (2) a malalignment type of ventricular septal defect (VSD); (3) dextroposition of the aorta so that it overrides the ventricular septum; and (4) right ventricular hypertrophy (RVH; Fig. 479.1). Obstruction to pulmonary artery blood flow is usually at both the RV infundibulum (subpulmonic area) and the pulmonary valve. The main pulmonary artery (MPA) may also be small, and various degrees of branch pulmonary artery stenosis may be present. Complete obstruction of RV outflow (tetralogy with pulmonary atresia) is classified as an *extreme* form of tetralogy of Fallot (see Chapter 479.2) and may be associated with various degrees of hypoplasia of the branch pulmonary arteries. The degree of pulmonary outflow obstruction and whether the ductus arteriosus is open or closed determine the degree of the patient's cyanosis and the age at first presentation.

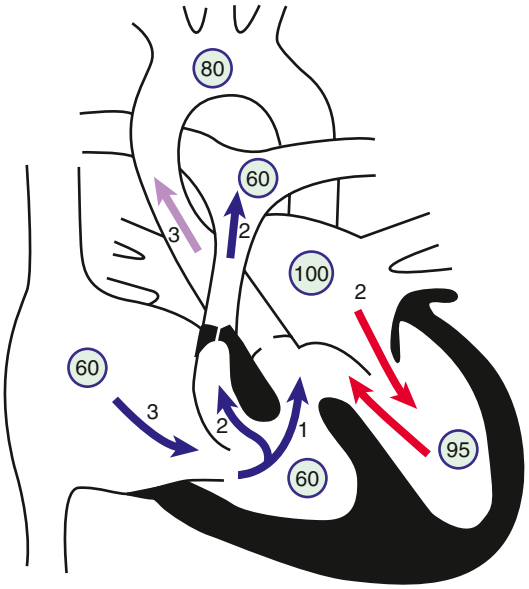

Fig. 479.1 Physiology of tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). Atrial (mixed venous) oxygen saturation is decreased because of the systemic hypoxemia. A volume of 3 L/min/m^2 of desaturated blood enters the right atrium and traverses the tricuspid valve. Two liters flow through the right ventricular outflow tract into the lungs, whereas 1 L shunts right to left through the ventricular septal defect (VSD) into the ascending aorta. Thus pulmonary blood flow is two-thirds normal (Qp:Qs [pulmonary-to-systemic blood flow ratio] of 0.7:1). Blood returning to the left atrium is fully saturated. Only 2 L of blood flow across the mitral valve. Oxygen saturation in the left ventricle may be slightly decreased because of right-to-left shunting across the VSD. Two liters of saturated left ventricular blood mixing with 1 L of desaturated right ventricular blood are ejected into the ascending aorta. Aortic saturation is decreased, and cardiac output is normal.

PATHOPHYSIOLOGY

The pulmonary valve annulus may range from being nearly normal in size to being severely hypoplastic. The valve itself is often bicuspid or unicuspid and, occasionally, is the only site of stenosis. More often, the subpulmonic or infundibular muscle, known as the *crista supraventricularis,* is hypertrophic, which contributes to the subvalvar stenosis and results in an infundibular chamber of variable size and contour. When the right ventricular outflow tract (RVOT) is completely obstructed **(pulmonary atresia)**, the anatomy of the branch pulmonary arteries is extremely variable. An MPA segment may be in continuity with RV outflow, separated by a fibrous but imperforate pulmonary valve; the MPA may be moderately or severely hypoplastic but still supply part or all of the pulmonary bed; or the entire main pulmonary artery segment may be absent. Occasionally, the branch pulmonary arteries may be discontinuous. In these extreme cases, pulmonary blood flow may be supplied by a **patent ductus arteriosus** (PDA) or by multiple **major aortopulmonary collateral arteries (MAPCAs)** arising from the ascending and/or descending aorta or aortic branches and supplying various lung segments.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps. Rarely, the VSD may be in the inlet portion of the ventricular septum (tetralogy with atrioventricular septal defect). The normal fibrous continuity of the mitral and aortic valves is usually maintained, and if not (because of the presence of a subaortic muscular conus), the defect is classified as a **double-outlet right ventricle** (DORV) instead of tetralogy of Fallot (see Chapter 479.5). The aortic arch is right sided in 20% of cases, and the aortic root is usually large and overrides the VSD to varying degrees. When the aorta overrides the VSD by >50% (in which case it may also be a subaortic conus), this defect is also classified as a form of DORV; however, the circulatory dynamics and the method of repair for these types of DORV are the same as for tetralogy of Fallot.

Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts in the presence of marked pulmonary stenosis, blood is shunted into the overriding aorta or across the VSD into the aorta. Persistent arterial desaturation and cyanosis result, with the degree of desaturation dependent on the severity of the pulmonary obstruction. Pulmonary blood flow, when severely restricted by the obstruction to RV outflow, is often supplemented by a PDA during the immediate newborn period. Peak systolic and diastolic pressures in each ventricle are similar and at the systemic level. A large pressure gradient occurs across the obstructed RVOT, and pulmonary artery pressure is either normal or lower than normal. The degree of RV outflow obstruction determines the timing of the onset of symptoms and the severity of cyanosis. When obstruction to RV outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic (**acyanotic** or "pink" tetralogy of Fallot). When obstruction is severe, cyanosis will be present from birth and worsen dramatically when the ductus arteriosus begins to close.

CLINICAL MANIFESTATIONS

Infants with mild degrees of RV outflow obstruction may initially even have symptoms of heart failure caused by a ventricular-level left-to-right shunt. In these patients, cyanosis is not present at birth, but with increasing hypertrophy of the RV infundibulum as the patient grows, cyanosis occurs later in the first few months of life. In contrast, in infants with more severe degrees of RV outflow obstruction, neonatal cyanosis is noted immediately. In these infants, pulmonary blood flow

may be partially or almost totally dependent on flow through the ductus arteriosus. When the ductus begins to close in the first few hours or days of life, severe cyanosis and circulatory collapse may occur. All degrees of variation exist between these two clinical extremes. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, mucous membranes, and nailbeds (the latter two are key to diagnosing cyanosis in children with darker skin color). Patients may have gray sclerae with engorged blood vessels and (usually after 2 years of age) clubbing of the fingers and toes. Chapter 483 describes the extracardiac manifestations of long-standing cyanotic congenital heart disease.

In older children with unrepaired tetralogy, dyspnea occurs on minimal exertion. They may play actively for a short time and then sit or lie down or walk a block or so before stopping to rest. Characteristically, children assume a **squatting** position for the relief of dyspnea caused by physical effort; squatting increases venous return to the right side of the heart and also increases systemic vascular resistance, both serving to increase flow through the obstructed RV outflow. The child is usually able to resume physical activity after a few minutes of squatting.

Paroxysmal hypercyanotic attacks (hypoxic, "blue," or "tet" spells) may develop during the first year of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the typical systolic ejection murmur occurs as flow across the RVOT diminishes during the spell. Tet spells may last from a few minutes to a few hours. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness and occasionally to convulsions, stroke, and death. The onset of these spells is usually spontaneous and unpredictable. They are associated with reduction of an already compromised pulmonary blood flow, which, when prolonged, results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest may be more prone to the development of hypoxic spells because they have not acquired the homeostatic mechanisms that would allow them to better tolerate rapid lowering of arterial oxyhemoglobin saturation (Sao_2), such as polycythemia.

Depending on the frequency and severity of hypercyanotic attacks, one or more of the following procedures should be instituted in sequence: (1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant's clothing is not constrictive; (2) administration of oxygen (although increasing inspired oxygen will not reverse cyanosis caused by intracardiac shunting); (3) injection of morphine subcutaneously or intranasal fentanyl or intranasal midazolam; (4) administer propranolol or esmolol; and (5) begin a phenylephrine intravenous infusion. Calming and holding the infant in a knee-chest position may abort progression of an early spell. Premature attempts to obtain blood samples may cause further agitation and may be counterproductive; transcutaneous oxygen saturation monitoring is helpful in these cases but is limited in not measuring the degree of acidosis if the spell is prolonged.

Because metabolic acidosis develops when arterial oxygen tension (Pao_2) is <40 mm Hg, rapid correction (within several minutes) with intravenous (IV) administration of sodium bicarbonate is necessary if the spell is unusually severe and the child shows a lack of response to the foregoing therapy. Recovery from the spell is usually rapid once the pH has returned to normal. Repeated blood pH measurements may be necessary because rapid recurrence of acidosis may ensue. For spells that are resistant to this therapy, intubation and anesthetic sedation are often sufficient to break the spell. Drugs that increase systemic vascular resistance, such as IV phenylephrine, can improve RV outflow, decrease the right-to-left shunt, and improve symptoms. β-Adrenergic blockade by the IV administration of propranolol (0.15-0.25 mg/kg/dose given slowly; can be repeated once in 15 minutes) has also been used. Spells are quite rare because most infants with tetralogy of Fallot undergo reparative surgery in early infancy.

Growth and development may be delayed in patients with severe untreated tetralogy of Fallot, particularly when their Sao_2 is chronically <70%. Puberty may also be delayed in patients who have not undergone surgery.

The peripheral pulses are usually normal, as are central venous and arterial pressures. In older infants and children, the left anterior hemithorax may bulge anteriorly because of long-standing RVH. A substernal RV impulse can usually be detected. A systolic thrill may be felt along the left sternal border in the third and fourth parasternal spaces. The systolic murmur is usually loud and harsh; it may be transmitted widely, especially to the lungs, but is most intense at the mid- and upper-left sternal border. The murmur is generally ejection in quality at the upper-left sternal border, but it may sound more holosystolic toward the lower-left sternal border. It may be preceded by a click at the upper sternal border or over the sternum. The murmur is caused by turbulence through the RVOT. It tends to become louder, longer, and harsher as the severity of pulmonary stenosis increases from mild to moderate; however, it can become less prominent with severe obstruction, especially during a hypercyanotic spell, because of shunting of blood away from the RV outflow through the overriding aortic valve. Either the second heart sound (S_2) is single or the pulmonic component is soft because of the decreased excursion of the stenotic valve. Infrequently, a continuous murmur may be audible, especially if prominent MAPCAs are present.

DIAGNOSIS

The typical radiologic configuration as seen in the anteroposterior (AP) view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal overall heart size. The hypertrophied right ventricle causes the rounded apical shadow to be uptilted so that it is situated higher above the diaphragm than normal and pointing horizontally to the left chest wall. The cardiac silhouette has been likened to that of a *boot* ("coeur en sabot") (Fig. 479.2). The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in approximately 20% of patients it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the AP view.

The electrocardiogram (ECG) demonstrates right-axis deviation and evidence of RVH; because prominent right-sided forces are normal in the newborn period, the ECG may be technically normal at this time. A dominant R wave appears in the right precordial chest leads (V_1, V_2) or an RSR′ pattern. In some cases, the only sign of RVH may initially

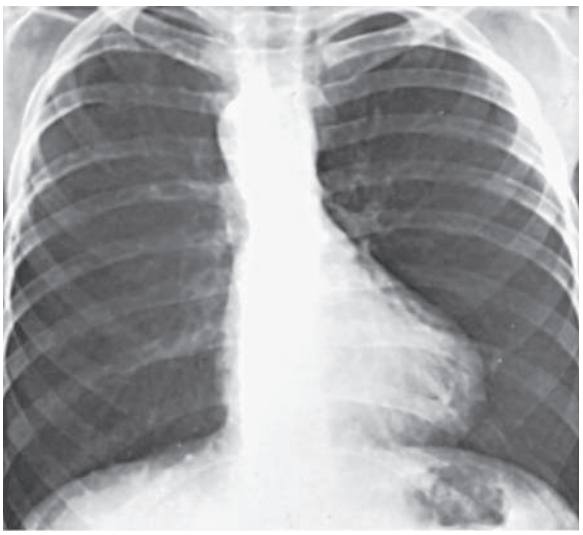

Fig. 479.2 Chest radiograph of 8-yr-old child with tetralogy of Fallot. Note the normal heart size, some elevation of the cardiac apex, concavity in the region of the main pulmonary artery, right-sided aortic arch, and diminished pulmonary vascularity.

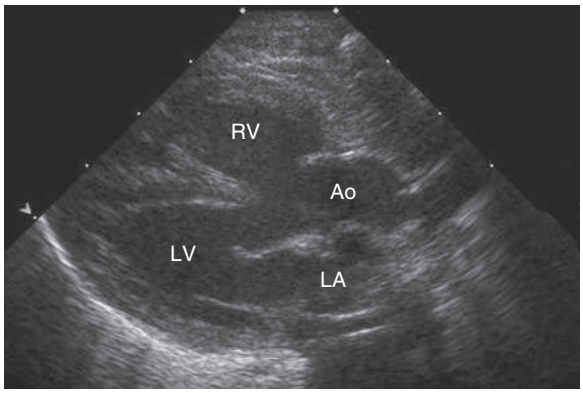

Fig. 479.3 Echocardiogram of patient with tetralogy of Fallot. This parasternal long-axis 2D view demonstrates anterior displacement of the outflow ventricular septum that resulted in stenosis of the subpulmonic right ventricular outflow tract, overriding of the aorta, and an associated ventricular septal defect. Ao, Overriding aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

be a positive T wave in leads V_3R and V_1. The P wave may be tall and peaked, suggesting right atrial enlargement (see Fig. 472.6).

Two-dimensional (2D) echocardiography with Doppler establishes the diagnosis (Fig. 479.3) and provides information about the extent of aortic override of the septum, the location and degree of the RVOT obstruction, the size of the pulmonary valve annulus and main and proximal branch pulmonary arteries, and the side of the aortic arch. The echocardiogram is also useful in determining whether a PDA is supplying a portion of the pulmonary blood flow. In a patient with tetralogy of Fallot without pulmonary atresia, echocardiography usually obviates the need for catheterization before surgical repair. However, in patients with pulmonary atresia, catheterization and CT angiography are usually necessary to image the size and source of blood supply (native pulmonary arteries or MAPCAs) to each lung vascular segment.

Cardiac catheterization demonstrates a systolic pressure in the right ventricle equal to the systemic pressure because the right ventricle is connected directly to the overriding aorta. If the pulmonary artery is entered, the pressure is greatly decreased, although crossing the RVOT, especially in severe cases, may precipitate a tet spell. Pulmonary artery pressure is usually lower than normal, in the range of 5-10 mm Hg. The Sao_2 level depends on the magnitude of the right-to-left shunt; in "pink tets," the systemic So_2 may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75–85%.

Selective right ventriculography will demonstrate all the anatomic features. Contrast medium outlines the heavily trabeculated right ventricle. The infundibular stenosis varies in length, width, contour, and distensibility (Fig. 479.4). The pulmonary valve is usually thickened, and the annulus may be small. In patients with tetralogy and pulmonary atresia, echocardiography alone is not adequate to assess the anatomy of the true pulmonary arteries and collateral MAPCAs. Cardiac CT is extremely helpful, and cardiac catheterization with injection into each arterial collateral is usually indicated. Complete and accurate information regarding the size and peripheral distribution of the main pulmonary arteries and any collateral vessels (MAPCAs) is important when evaluating these children for complex reparative surgery.

Aortography or coronary arteriography outlines the course of the coronary arteries. In 5–10% of patients with the tetralogy of Fallot, coronary artery abnormalities may be present, most often an aberrant coronary artery crossing over the RVOT; care must be taken not to cut this artery during surgical repair. Verification of normal coronary arteries is important when considering surgery in young infants, who may need a patch across the pulmonary valve annulus. Echocardiography can usually delineate the coronary artery anatomy; angiography is reserved for cases in which questions remain.

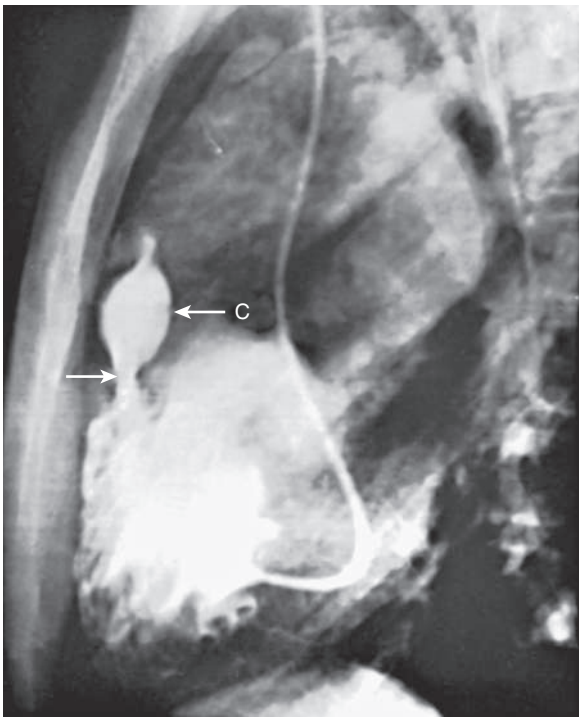

Fig. 479.4 Lateral view of selective right ventriculogram in patient with tetralogy of Fallot. The *left arrow* points to an infundibular stenosis that is below the infundibular chamber (C). The narrowed pulmonary valve orifice is seen at the distal end of the infundibular chamber.

COMPLICATIONS

Before the advent of corrective surgery, patients with tetralogy of Fallot were susceptible to several serious complications. For this reason, most children undergo complete repair (or in rare situations palliation) in the first few months of life; consequently, these complications are now rare. **Cerebral thromboses**, usually occurring in the cerebral veins or dural sinuses and occasionally in the cerebral arteries, are sequelae of extreme polycythemia and dehydration. Thromboses occur most often in patients younger than 2 years. These patients may have iron-deficiency anemia, frequently with hemoglobin and hematocrit levels in the normal range (but too low for cyanotic heart disease). Therapy consists of adequate hydration and supportive measures. Phlebotomy and volume replacement with albumin or saline are indicated in extremely polycythemic patients who are symptomatic.

Brain abscess is less common than cerebrovascular events and extremely rare today. Patients with a brain abscess are usually older than 2 years. The onset of the illness is often insidious and consists of low-grade fever or a gradual change in behavior, or both. Some patients have an acute onset of symptoms that may develop after a recent history of headache, nausea, and vomiting. Seizures may occur; localized neurologic signs depend on the site and size of the abscess and the presence of increased intracranial pressure. Head CT or MRI confirms the diagnosis. Antibiotic therapy may help keep the infection localized, but surgical drainage of the abscess is usually necessary (see Chapter 644).

Bacterial endocarditis may occur in the RV infundibulum or on the pulmonic, aortic, or rarely, tricuspid valve. Endocarditis may complicate palliative shunts or, in patients with corrective surgery, any residual pulmonic stenosis or VSD. Heart failure is not a usual feature in patients with tetralogy of Fallot, with the exception of some young infants with "pink" or acyanotic tetralogy of Fallot. When the degree of pulmonary obstruction worsens with age, the symptoms of heart failure resolve, and eventually the patient experiences cyanosis, usually by 4-6 months of age. These patients are at increased risk for hypercyanotic spells at this time.

ASSOCIATED ANOMALIES

A PDA may be present, and defects in the atrial septum are occasionally seen. A right aortic arch occurs in approximately 20% of patients, and other anomalies of the pulmonary arteries and aortic arch may also be seen. Persistence of a left superior vena cava draining into the coronary sinus is common but not a concern. Multiple VSDs are occasionally present and should be diagnosed before corrective surgery. Coronary artery anomalies are present in 5–10% and can complicate surgical repair. Tetralogy of Fallot may also occur with an atrioventricular septal defect, often associated with Down syndrome.

Congenital absence of the pulmonary valve produces a distinct syndrome that is usually marked by signs of upper airway obstruction (see Chapter 477.1). Cyanosis may be absent, mild, or moderate; the heart is large and hyperdynamic; and a loud to-and-fro murmur is present. Marked aneurysmal dilation of the main and branch pulmonary arteries results in compression of the bronchi and then produces stridulous or wheezing respirations and recurrent pneumonia. If the airway obstruction is severe, reconstruction of the trachea at the time of corrective cardiac surgery may be required to alleviate the symptoms.

Absence of a branch pulmonary artery, most often the left, should be suspected if the radiographic appearance of the pulmonary vasculature differs between the right and left sides; absence of a pulmonary artery is often associated with hypoplasia of the affected lung. It is important to recognize the absence of a pulmonary artery because occlusion of the remaining pulmonary artery during surgery seriously compromises the already reduced pulmonary blood flow.

As one of the conotruncal malformations, tetralogy of Fallot can be associated with **DiGeorge syndrome** or **velocardiofacial syndrome**, also known by the acronym **CATCH 22** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization (FISH) demonstrates deletions of a large segment of **chromosome 22q11.2** known as the **DiGeorge critical region**. Deletion or pathogenic variants in *Tbx1* have been implicated as a possible cause of DiGeorge syndrome, although several other genes have been identified as possible candidates or as modifier genes (see Chapter 473).

TREATMENT

Treatment of tetralogy of Fallot depends on the severity of the RVOT obstruction. Infants with severe tetralogy require urgent medical treatment and surgical intervention in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. It is critical that normal body temperature be maintained during the transfer because cold increases oxygen consumption, which places additional stress on a cyanotic infant, whose oxygen delivery is already limited. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Neonates with marked RVOT obstruction may deteriorate rapidly because as the ductus arteriosus begins to close, pulmonary blood flow is further compromised. The IV administration of **prostaglandin E_1** (PGE_1; 0.05-0.1 μg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilation of the ductus arteriosus and usually provides adequate pulmonary blood flow until a surgical procedure can be performed. This agent should be administered intravenously as soon as cyanotic CHD is clinically suspected and continued through the preoperative period and during cardiac catheterization. Because prostaglandin can cause apnea, an individual skilled in neonatal intubation should be readily available.

Infants with less severe RVOT obstruction who are stable and awaiting surgical intervention require careful observation. Acyanotic patients can progress fairly quickly to having cyanotic episodes. Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. In the past, oral propranolol (0.5-2 mg/kg every 6 hours) was used to decrease the frequency and severity of hypercyanotic spells, but with the excellent surgical results available today, surgical treatment is indicated, usually before spells begin.

Infants with symptoms and severe cyanosis in the first month of life usually have marked obstruction of the RVOT. Two options are available in these infants. The first option is **corrective open heart surgery** performed in early infancy (or even in the newborn period in critically ill infants). This approach has widespread acceptance with excellent short- and long-term results and has supplanted palliative shunts (see later) for most cases. Early total repair carries the theoretical advantage that early physiologic correction allows for improved growth of the branch pulmonary arteries. In infants with less severe cyanosis who can be maintained with good growth and absence of hypercyanotic spells, primary repair is performed electively in the first few months.

Corrective surgical therapy consists of relief of the RVOT obstruction by resecting obstructive muscle bundles and by patch closure of the VSD. If the pulmonary valve is stenotic, as it usually is, a valvotomy is performed. If the pulmonary valve annulus is too small or the valve is extremely thickened, a valvectomy may be performed, the pulmonary valve annulus split open, and a transannular patch placed across the pulmonary valve ring. The advantage of a patch that is not circumferential is that it preserves part of the normal valve annulus and leaflets, allowing for future growth. A right ventriculotomy was once the standard approach; a transatrial-transpulmonary approach is routinely performed to reduce the long-term risks of a large right ventriculotomy. In the past, surgeons placed large transannular patches with the goal of eliminating any possibility of residual pulmonary stenosis, even if these resulted in wide-open pulmonary insufficiency. Currently, surgeons use smaller patches and are more accepting of small RVOT gradients if the degree of valve insufficiency can be minimized. In tetralogy patients, pulmonary valve insufficiency is one of the main reasons for reoperation long-term.

The second option, rarely used today, is a palliative systemic-to-pulmonary artery shunt **(Blalock-Taussig or B-T shunt)** performed to augment pulmonary artery blood flow. The B-T shunt augmented pulmonary blood flow, decreasing hypoxia, improving linear growth, and augmenting growth of the branch pulmonary arteries. Initially performed via direct anastomosis of the subclavian artery to the pulmonary artery, today, the modified B-T shunt consists of a Gore-Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery (Fig. 479.5). Sometimes the shunt is brought directly from the ascending aorta to the MPA; in this case it is called a *central shunt*. Postoperative complications after a B-T shunt include chylothorax, diaphragmatic paralysis, and Horner syndrome. Rarely, postoperative pulmonary overcirculation leading to symptoms of cardiac failure may be caused by too large a shunt. Long-term problems associated with the original B-T shunt (absent radial pulse and arm length discrepancy) are rarely seen with the current procedure.

B-T shunts are usually reserved for patients with comorbidities, such as other major congenital anomalies or prematurity, that would make full repair a higher-risk option. Many surgeons still recommend full repair in these situations, being preferable to the combined risks of a staged procedure, and successful complete repairs have been done even in small premature infants.

PROGNOSIS

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Uncommon immediate postoperative problems include RV failure, transient heart block, residual VSD with left-to-right shunting, and (rarely) myocardial infarction from interruption of an aberrant coronary artery. The long-term effects of isolated, surgically induced pulmonary valvular insufficiency or of insufficiency and mild stenosis (as is more typical with modern-era smaller transannular patches) are still being defined as more patients with repaired tetralogy of Fallot reach adulthood, but pulmonary insufficiency is generally well tolerated through childhood and early adolescence. Many patients after tetralogy repair, and all those with transannular patch repairs, have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild

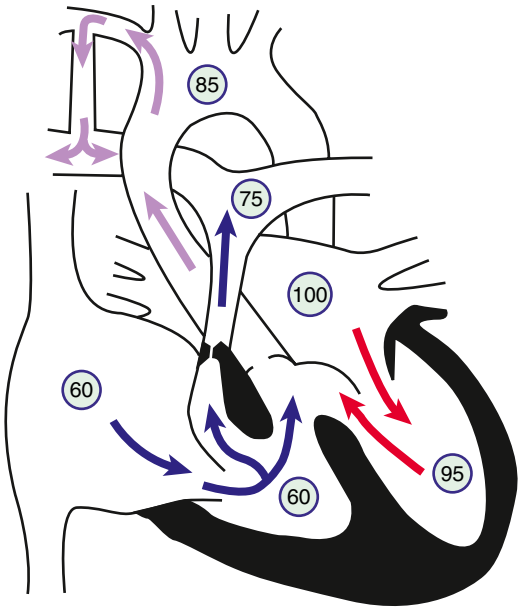

Fig. 479.5 Physiology of Blalock-Taussig shunt in patient with tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The intracardiac shunting pattern is as described for Figure 479.1. Blood shunting left to right across the shunt from the right subclavian artery to the right pulmonary artery increases total pulmonary blood flow and results in a higher oxygen saturation than would exist without the shunt.

to moderate pulmonary insufficiency. Patients with more marked or long-standing pulmonary valve insufficiency may also have moderate to more severe degrees of RV enlargement and may develop tricuspid regurgitation as the tricuspid valve annulus dilates. These patients will develop a holosystolic murmur at the lower-left and -right sternal borders. Patients with a moderate to severe residual gradient (stenosis) across the RVOT usually require balloon angioplasty or catheter placement of a stent or reoperation, but milder degrees of residual obstruction usually do not require reintervention.

Follow-up of patients 5-20 years after surgery indicates generally excellent outcomes, with minimal symptoms and good exercise tolerance. Despite being asymptomatic, many patients may have lower-than-normal exercise capacity and maximal heart rate on formal cardiopulmonary exercise testing. These abnormal findings are more common in patients who underwent placement of a transannular outflow tract patch and may be less frequent when surgery is performed at an early age. When these children move into adolescence and adulthood, some (more often those with transannular patches) will develop RV dilation as a result of long-term pulmonary regurgitation. Careful surveillance for excessive RV dilation and early signs of RV dysfunction is critical. After reaching adulthood, lifelong follow-up by a specialist in adult congenital heart disease (CHD) is important. Serial echocardiography and the more quantitative magnetic resonance angiography (MRI/MRA) are valuable tools for assessing the degree of RV dilation, identifying the presence of early stages of RV dysfunction, and quantifying the regurgitant fraction. A significant portion of patients with tetralogy of Fallot have been found to have some degree of fibrosis within the right ventricle by MRI. Valve repair or replacement is indicated for those patients with increasing RV dilation and if tricuspid regurgitation is more than mild. For patients requiring valve replacement, nonsurgical (transcatheter) options are available. Several stent-valves can be delivered in the cardiac catheterization laboratory, and these have been used successfully in patients with repaired tetralogy of Fallot. The initial versions of these devices (the Melody valve) were designed to be used predominantly in patients who have previously had a homograft or other artificial conduit placed between the RV and pulmonary arteries; often stent-valves (the Harmony valve) have been designed to be inserted into the native RVOT.

Conduction disturbances can occur after surgery. The atrioventricular node and the bundle of His and its divisions are close to the VSD and may be injured during surgery; however, permanent complete heart block after tetralogy repair is rare. When present, it should be treated by placement of a permanently implanted pacemaker. Even transient complete heart block in the immediate postoperative period is rare; it may be associated with an increased incidence of late-onset complete heart block and sudden death. In contrast, right bundle branch block is extremely common on the postoperative ECG. The duration of the QRS interval has been shown to predict both the presence of residual hemodynamic derangement and the long-term risk of arrhythmia (mainly ventricular tachycardia) and sudden death. Biventricular pacing (in which a pacemaker is used to resynchronize the activation of the right and left ventricles) has been shown to improve hemodynamics in patients with RV dysfunction and long ventricular conduction delays on ECG.

Many children have **premature ventricular beats** after repair of the tetralogy of Fallot. These beats, if isolated and infrequent, may be benign but are of particular concern in patients with residual hemodynamic abnormalities. Approximately 10% of patients with repaired tetralogy are at risk of life-threatening ventricular arrhythmias, and 30% are at risk of atrial arrhythmias as they reach adulthood. Long-duration electrocardiographic monitoring studies, such as Holter (24-48 hours) or ZioPatch (1-2 weeks), should be performed on a regular basis to ensure that occult episodes of ventricular tachycardia are not occurring. Exercise studies may be useful in provoking cardiac arrhythmias that are not apparent at rest. In the presence of complex ventricular arrhythmias or severe residual hemodynamic abnormalities, prophylactic antiarrhythmic drug therapy or an implantable defibrillator is warranted. Surgical or transcatheter intervention is indicated if significant residual RVOT obstruction or severe pulmonary insufficiency is present because arrhythmia risk may improve after hemodynamics are restored to a more normal level.

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479.2 Tetralogy of Fallot with Pulmonary Atresia

Daniel Bernstein

Tetralogy of Fallot with pulmonary atresia is the most extreme form of the tetralogy of Fallot. The pulmonary valve is atretic (absent), and the pulmonary trunk may be hypoplastic or atretic as well. The entire RV output is ejected into the aorta. Pulmonary blood flow is then dependent on multiple **major aortopulmonary collateral arteries (MAPCAs)** arising from the ascending and/or descending aorta or aortic branches and supplying various lung segments or, rarely, on a PDA. The ultimate prognosis depends on the presence or absence of true branch pulmonary arteries and, if present, the degree of development. This is best assessed by a combination of CT and cardiac catheterization. If repair is approached early in life and performed at a center with expertise in this highly complex surgery, the mid-term outcomes are good. However, if the pulmonary arteries are severely hypoplastic and surgical intervention fails to establish low pulmonary vascular pressures, lung or heart-lung transplantation may be the only therapy (see Chapter 492.2). Tetralogy of Fallot with pulmonary atresia is also associated with the 22q11.2 deletion and DiGeorge syndrome. The association of severe **tracheomalacia** or **bronchomalacia** with these severe forms of tetralogy/pulmonary atresia may complicate postoperative recovery.

CLINICAL MANIFESTATIONS

Patients with tetralogy of Fallot/pulmonary atresia have findings similar to those in patients with severe tetralogy of Fallot. Cyanosis usually appears within the first few hours or days after birth; however, the prominent systolic murmur associated with tetralogy is usually absent. The first heart sound (S_1) may be followed by an ejection click caused

by the enlarged aortic root, S_2 is single and loud, and continuous murmurs of collateral flow may be heard over the entire precordium and over the back. Most patients are moderately cyanotic and are initially stabilized with a PGE_1 infusion pending cardiac catheterization and/or CT scan to further delineate the anatomy. Patients with several large MAPCAs may be less cyanotic and, once the diagnosis is confirmed, can be taken off prostaglandin while awaiting palliative surgical intervention. Some patients may even develop symptoms of heart failure caused by increased pulmonary blood flow via these collateral vessels.

DIAGNOSIS

The chest radiograph demonstrates a varying heart size, depending on the amount of pulmonary blood flow, a concavity at the position of the pulmonary arterial segment, and often the reticular pattern of bronchial collateral flow. The ECG shows RVH. The echocardiogram identifies aortic override, a thick RV wall, and atresia of the pulmonary valve. Pulsed and color Doppler echocardiographic studies show an absence of forward flow across the pulmonary valve, with pulmonary blood flow being supplied by MAPCAs, which can usually be seen using color Doppler arising from the descending aorta. At cardiac catheterization, right ventriculography reveals a large aorta, opacified immediately by passage of contrast medium through the VSD but with no dye entering the lungs through the RVOT. It is important in planning surgical repair to delineate carefully the often diminutive native pulmonary arteries, if present, to determine whether they are continuous or discontinuous and whether they arborize to all lung segments. The location and arborization of all MAPCAs and the presence of any localized stenosis, which become more common as the patient grows older, are determined by selective contrast injection into each vessel from its origin in the aorta. CT angiography is extremely valuable in mapping the extent of MAPCA arborization.

TREATMENT

The surgical procedure of choice depends on whether the MPA segment is present and, if so, on the size and branching pattern of the branch pulmonary arteries. If these arteries are well developed, a one-stage surgical repair with a homograft conduit inserted between the right ventricle and pulmonary arteries and closure of the VSD is usually feasible. If the pulmonary arteries are hypoplastic, extensive reconstruction may be required. This may involve several staged surgical procedures. If the native pulmonary artery is present but small, a connection made between the aorta and the hypoplastic native pulmonary artery **(aortopulmonary window)** can be performed in the newborn period to induce growth of the native pulmonary arteries. At 3-4 months of age, the multiple MAPCAs are gathered together **(unifocalization procedure)** and eventually incorporated into the final repair along with the native pulmonary arteries. This series of operations may be accomplished through successive right and left lateral thoracotomies or through a single midline sternotomy if the anatomy is favorable.

To be a candidate for full repair, the pulmonary arteries must be of adequate size to accept the full volume of RV output. Complete repair includes closure of the VSD and placement of a homograft conduit from the right ventricle to the pulmonary artery. At the time of reparative surgery, previous shunts are taken down. Because of patient growth and homograft narrowing caused by proliferation of intimal tissue and calcification, replacement of the homograft conduit replacement is usually required in later life, and multiple replacements may be needed. Some of these patients are candidates for placement of a transcatheter stent-valve in the pulmonary position. Patients with obstruction of the very distal branches of the pulmonary arteries may undergo repeat surgical procedures or transcatheter balloon dilation and stenting of the multibranch pulmonary arterial stenosis. Careful follow-up is warranted for these patients, with a combination of echocardiogram, catheterization, and CT or MRI, to ensure maximal chance of growth of all pulmonary artery segments. Serial radionuclide lung perfusion scans can be used to assess pulmonary perfusion to each lung segment and the percentage of flow to the right vs the left lung.

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479.3 Pulmonary Atresia with Intact Ventricular Septum

Daniel Bernstein

Pulmonary atresia with an intact ventricular septum presents in the newborn period with severe cyanosis. The pulmonary valve leaflets are completely fused to form a membrane, and the RVOT is atretic. Because no VSD is present, no egress of blood from the right ventricle can occur. Any blood that enters the right ventricle will regurgitate back across the tricuspid valve into the right atrium. Right atrial pressure increases, and blood shunts via the foramen ovale into the left atrium, where it mixes with pulmonary venous blood and enters the left ventricle (Fig. 479.6). The combined left and right ventricular output is pumped solely by the left ventricle into the aorta. In a newborn with pulmonary atresia, the only source of pulmonary blood flow occurs via a PDA. The right ventricle and tricuspid valve are usually hypoplastic, although the degree of hypoplasia varies considerably. Patients who have a small RV cavity also tend to be those with the smallest tricuspid valve annulus, which limits RV inflow. Patients with pulmonary atresia and intact ventricular septum may have **coronary sinusoidal channels** within the RV wall that communicate directly with the coronary arterial circulation. The high RV pressure results in desaturated blood flowing retrograde through these channels into the coronary arteries. Sometimes there are also stenoses of the coronary arteries proximal to where the sinusoids enter, so that distal coronary artery flow is dependent on flow from the right ventricle (known as *right ventricle–dependent coronary circulation*). The prognosis in patients with these sinusoids and proximal stenosis of the coronary arteries is more guarded than in those patients without sinusoids or with sinusoids but no coronary stenoses. Rarely, the proximal coronary artery may be totally absent.

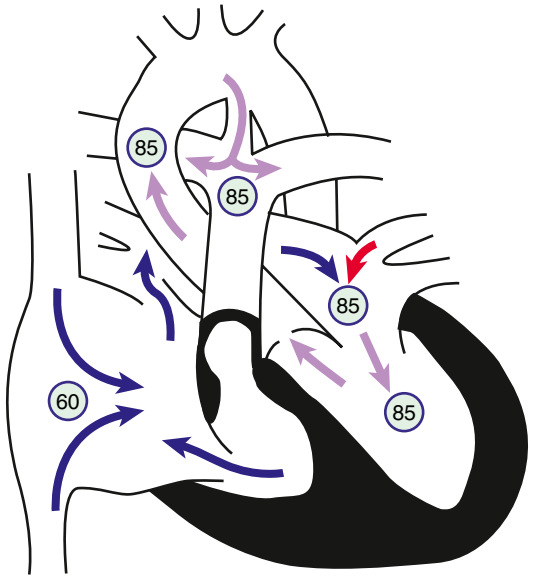

Fig. 479.6 Physiology of pulmonary atresia with intact ventricular septum. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. A small amount of the blood entering the right atrium may cross the tricuspid valve, which is often stenotic as well. The right ventricular cavity is hypertrophied and may be hypoplastic. No outlet from the right ventricle exists because of the atretic pulmonary valve; thus any blood entering the right ventricle returns to the right atrium via tricuspid regurgitation. Most of the desaturated blood shunts right to left via the foramen ovale into the left atrium, where it mixes with fully saturated blood returning from the lungs. The only source of pulmonary blood flow is via the patent ductus arteriosus. Aortic and pulmonary arterial oxygen saturation will be identical (definition of a total mixing lesion).

CLINICAL MANIFESTATIONS

When the ductus arteriosus closes in the first hours or days of life, infants with pulmonary atresia and an intact ventricular septum become markedly cyanotic because their only source of pulmonary blood flow is removed. Untreated, most patients die within the first week of life. Physical examination reveals severe cyanosis and respiratory distress. S_2, representing only aortic closure, is single and loud. Often, no murmurs are audible; sometimes a systolic or continuous murmur can be heard secondary to ductal blood flow. A harsh holosystolic murmur may be heard at the lower left and right sternal borders if there is significant tricuspid regurgitation.

DIAGNOSIS

The ECG shows a frontal QRS axis between 0 and +90 degrees, the amount of leftward shift reflecting the degree of RV hypoplasia. Tall, spiked P waves indicate right atrial enlargement. QRS voltages are consistent with left ventricular dominance or hypertrophy; RV forces are usually decreased in proportion to the decreased size of the RV cavity. Because the normal newborn ECG shows increased right-sided forces, if a normal "adult" ECG R-wave progression is seen, it suggests RV hypoplasia of some degree. Most patients with small right ventricles have decreased RV forces, but occasionally, patients with larger, thickened RV cavities may have evidence of RVH. The chest radiograph shows decreased pulmonary vascularity, the degree depending on the size of the branch pulmonary arteries and the patency of the ductus. Unlike in patients with pulmonary atresia and tetralogy of Fallot, the presence of MAPCAs is rare.

The 2D echocardiogram is useful in estimating RV dimensions and the size of the tricuspid valve annulus, which have been shown to be of prognostic value. Echocardiography can often suggest the presence of sinusoidal channels but cannot be used to evaluate coronary stenoses. Thus cardiac catheterization is necessary for complete evaluation. Pressure measurements reveal right atrial and RV hypertension. Ventriculography demonstrates the size of the RV cavity, the atretic RVOT, the degree of tricuspid regurgitation, and the presence or absence of intramyocardial sinusoids filling the coronary vessels. Aortography shows filling of the pulmonary arteries by the PDA and is helpful in determining the size and branching patterns of the pulmonary arterial bed. An aortogram or, if necessary, selective coronary angiography is performed to evaluate for the presence of proximal coronary artery stenosis (RV-dependent coronary circulation) or proximal coronary artery atresia.

TREATMENT

Infusion of PGE_1 (0.05-0.1 μg/kg/min) is usually effective in keeping the ductus arteriosus open before intervention, thus reducing hypoxemia and acidemia before surgery. The choice of surgical procedure depends on whether there is an RV-dependent coronary circulation and on the size of the RV cavity. In patients with only mild to moderate RV hypoplasia without sinusoids, or in patients with sinusoids but no evidence of coronary stenoses, a surgical pulmonary valvotomy is carried out to relieve outflow obstruction. Often, the RVOT is widened with a patch. To provide adequate pulmonary blood flow, an aortopulmonary (Blalock-Taussig) shunt may also be performed during the same procedure. An alternative approach uses interventional catheterization, in which the imperforate pulmonary valve is first punctured either with a wire or a radiofrequency ablation catheter, followed by a balloon valvuloplasty. If this course is taken, it may take days to weeks before the RV muscle regresses enough for the patient to be weaned from prostaglandin, and many of these patients will still require surgical intervention.

The aim of surgery or interventional catheterization is to encourage growth of the RV chamber by allowing some forward flow through the pulmonary valve while using the shunt to ensure adequate pulmonary blood flow. Later, if the tricuspid valve annulus and RV chamber grow to adequate size, the shunt is taken down and any remaining atrial-level shunt can be closed. If the RV chamber remains too small for use as a pulmonary ventricle, the patient is treated as having a single-ventricle circulation, with a **Glenn procedure** followed by a modified **Fontan procedure** (see Chapter 479.4), allowing blood to bypass the hypoplastic right ventricle by flowing to the pulmonary arteries directly from the venae cavae. When coronary artery stenoses are present and retrograde coronary perfusion occurs from the right ventricle through myocardial sinusoids, the prognosis is more guarded because of a higher risk of arrhythmias, coronary ischemia, and sudden death. It is important for these patients not to try to open the RVOT, because dropping the RV pressure rapidly will reduce coronary perfusion, leading to ischemia. These patients are usually treated with an aortopulmonary shunt, followed by the Glenn and Fontan procedure. Although at higher risk than those without coronary stenoses, recent reports show good success with this approach; however, long-term complications are higher than in other groups of single-ventricle patients. A small number of these infants (e.g., those with atresia of a proximal coronary artery) are best referred for heart transplantation.

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479.4 Tricuspid Atresia

Daniel Bernstein

In tricuspid atresia, there is no outlet from the right atrium to the right ventricle; the entire systemic venous return leaves the right atrium and enters the left side of the heart through the foramen ovale or, most often, an atrial septal defect (ASD) (Fig. 479.7). The physiology of the circulation and the clinical presentation will depend on the presence and type of other congenital heart defects, most notably on whether the great arteries are normally related or are transposed (aorta arising from the right ventricle, pulmonary artery from the left ventricle). In patients with normally related great arteries, left ventricular (LV)

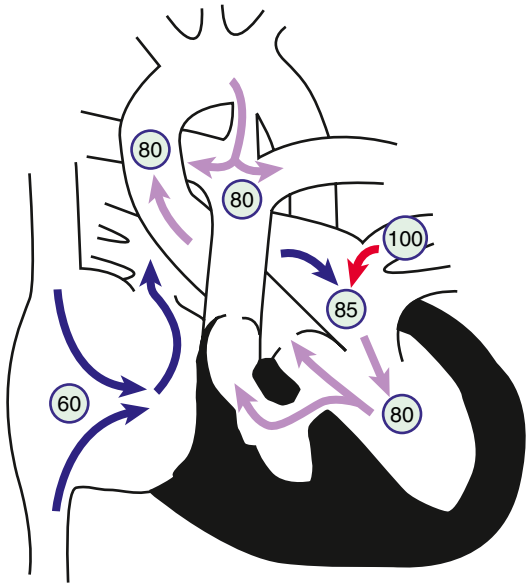

Fig. 479.7 Physiology of tricuspid atresia with normally related great vessels. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. The tricuspid valve is nonpatent, and the right ventricle may manifest varying degrees of hypoplasia. The only outlet from the right atrium involves shunting right to left across an atrial septal defect or patent foramen ovale to the left atrium. There, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected either through the aorta or via a ventricular septal defect (VSD) into the right ventricle. In this example, some pulmonary blood flow is derived from the right ventricle and the rest from a patent ductus arteriosus (PDA). In patients with tricuspid atresia, the PDA may close or the VSD may grow smaller and result in a marked decrease in systemic oxygen saturation.

blood supplies the systemic circulation through the aorta. Blood also flows into the right ventricle through a VSD (if the ventricular septum is intact, the right ventricle will be completely hypoplastic and pulmonary atresia will also be present [see Chapter 479.3]). *Pulmonary blood flow (and thus the degree of cyanosis) depends on the size of the VSD and the presence and severity of any associated pulmonic stenosis.* Pulmonary blood flow may be augmented by or be totally dependent on a PDA. The inflow portion of the right ventricle is always missing, but the outflow portion can be of variable size. The clinical presentation of patients with tricuspid atresia and *normally related great arteries* will depend on the degree of obstruction to pulmonary blood flow. Patients with a smaller VSD or moderate degrees of pulmonary stenosis are recognized in the early days or weeks of life by decreased pulmonary blood flow and cyanosis, especially after the PDA begins to close. Alternatively, in those with a large VSD and minimal or no RVOT obstruction, pulmonary blood flow may be normal or increased; these patients have only mild cyanosis and can present with signs of pulmonary overcirculation and heart failure.

In patients with tricuspid atresia and **transposition of the great arteries (TGA)**, LV blood flows directly into the pulmonary artery, whereas systemic blood must traverse the VSD and right ventricle to reach the aorta. In these patients, pulmonary blood flow is usually massively increased, and heart failure develops early. If the VSD is restrictive, systemic blood flow may be compromised and the patient may present with signs of decreased perfusion. **Coarctation of the aorta** is often noted in this setting.

CLINICAL MANIFESTATIONS

Some degree of cyanosis is usually evident at birth, with the extent depending on the degree of limitation to pulmonary blood flow. Unique to tricuspid atresia, an increased LV impulse may be noted, in contrast to most other causes of cyanotic heart disease, in which an increased RV impulse is usually present. Most patients have holosystolic murmurs audible along the left sternal border; S_2 is usually single. Pulses in the lower extremities may be weak or absent in the presence of transposition and with coarctation of the aorta. Patients with tricuspid atresia are at risk for spontaneous narrowing or even closure of the VSD, which can occasionally occur rapidly and lead to a marked increase in cyanosis.

DIAGNOSIS

Radiologic studies show either pulmonary undercirculation (most often in patients with normally related great arteries) or overcirculation (most often in patients with transposed great arteries). Left-axis deviation and LV hypertrophy are generally noted on the ECG (except in patients with TGA), and these unique features are a hallmark of tricuspid atresia, distinguishing it from most other cyanotic heart lesions, which are associated with right-axis deviation and RV hypertrophy. In the right precordial leads, the normally prominent R wave is replaced by an rS complex. The left precordial leads show a qR complex, followed by a normal, flat, biphasic, or inverted T wave. RV_6 is normal or tall, and SV_1 is generally deep. The P waves are usually biphasic, with the initial component tall and spiked in lead II. 2D echocardiography reveals the presence of a fibromuscular membrane in place of a tricuspid valve, a variably small right ventricle, variably sized VSD, and a slightly to moderately enlarged left ventricle (Fig. 479.8). The relationship of the great vessels (normal or transposed) can be determined. The degree of obstruction at the level of the VSD or at the RVOT can be determined by Doppler examination. Blood flow through a patent ductus can be evaluated by color flow and pulsed Doppler.

Cardiac catheterization, indicated usually only if questions remain after echocardiography, shows normal or slightly elevated right atrial pressure with a prominent *a* wave. If the right ventricle is entered through the VSD, the pressure may be lower than on the left if the VSD is restrictive in size. Right atrial angiography shows immediate opacification of the left atrium from the right atrium, followed by left ventricular filling and visualization of the aorta. Absence of direct flow to the right ventricle results in an angiographic filling defect between the right atrium and the left ventricle.

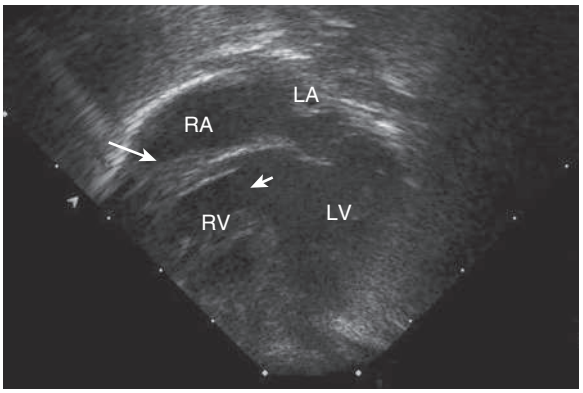

Fig. 479.8 Echocardiogram demonstrating tricuspid atresia. The floor of the right atrium consists of a fibromuscular membrane *(longer arrow)* instead of the normal tricuspid valve apparatus. The large secundum atrial septal defect can be seen between the right and left atria. The *short arrow* shows the ventricular septal defect. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT

Management of patients with tricuspid atresia depends on the adequacy of pulmonary blood flow. Moderately or severely cyanotic neonates (most often those with normally related great arteries) should be maintained on an IV infusion of PGE_1 (0.05-0.1 μg/kg/min) until a surgical aortopulmonary shunt procedure can be performed to increase pulmonary blood flow. The Blalock-Taussig procedure (see Chapter 479.1) or a variation is the preferred anastomosis. Rare patients with restrictive atrial-level communications also benefit from a Rashkind balloon atrial septostomy (see Chapter 480.2) or surgical septectomy.

Infants with increased pulmonary blood flow because of an unobstructed pulmonary outflow tract (more often patients with TGA) may require early surgery or pulmonary arterial banding (especially for patients in the first 1-2 months of life) to decrease the symptoms of heart failure and protect the pulmonary bed from the development of pulmonary vascular disease. Infants with just adequate pulmonary blood flow who are well balanced between cyanosis and pulmonary overcirculation can be watched closely for the development of increasing cyanosis, which may occur as the VSD begins to get smaller or the pulmonary outflow becomes narrower and is an indication for surgery.

The next stage of palliation for patients with tricuspid atresia involves the creation of an anastomosis between the superior vena cava and the pulmonary arteries (**bidirectional Glenn shunt**; Fig. 479.9A). This procedure is performed at usually between 2 and 6 months of age. The Glenn shunt provides a stable source of pulmonary blood flow as well as reducing the volume load on the left ventricle.

The **modified Fontan operation** is the preferred approach for longer-term palliation. It is usually performed between 2 and 3 years of age, after the patient is ambulatory. Initially, this procedure was performed by anastomosing the right atrium or atrial appendage directly to the pulmonary artery. The procedure used most often now is a modification of the Fontan procedure, known as a **cavopulmonary isolation procedure**, which involves anastomosing the inferior vena cava directly to the pulmonary arteries using a homograft or Gore-Tex tube running outside the heart (external-conduit Fontan; Fig. 479.9C). An older version of this procedure uses an internal baffle that runs along the lateral wall of the right atrium (lateral-tunnel Fontan; see Fig. 479.9B). In a completed Fontan repair, desaturated blood flows from both venae cavae directly into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the left ventricle, and is ejected into the systemic circulation. The volume load is completely removed from the left ventricle, and the right-to-left shunt is abolished. Because of the reliance on passive filling of the pulmonary circulation, the Fontan procedure is contraindicated in patients with elevated pulmonary vascular resistance, in those with pulmonary artery hypoplasia, and in patients with LV dysfunction. The patient also must not have significant mitral insufficiency. Patients who are not in normal sinus rhythm

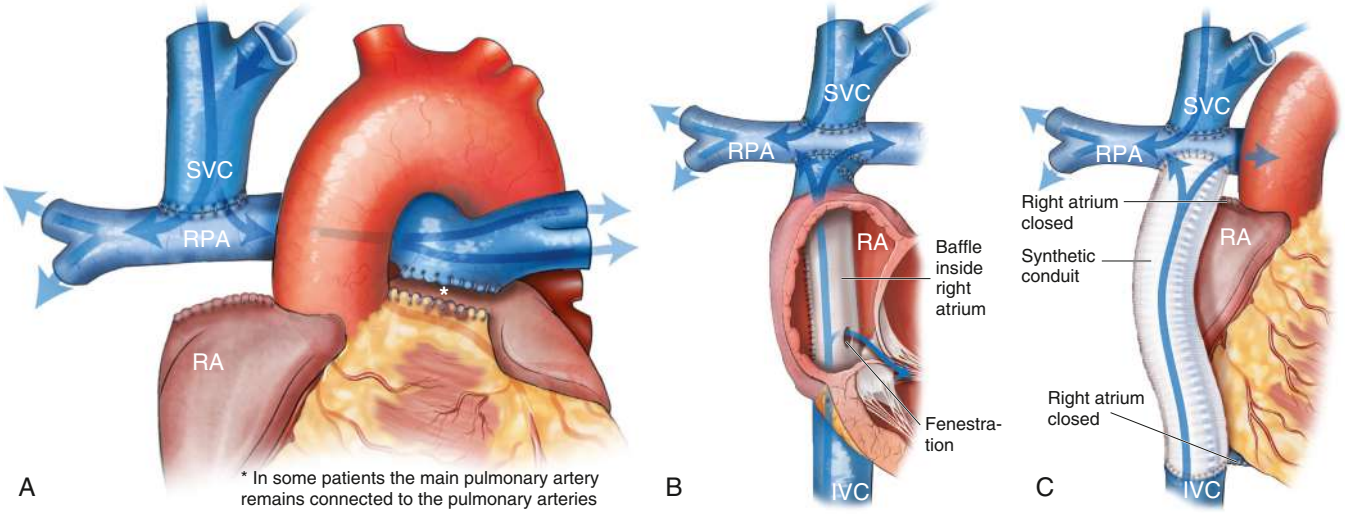

Fig. 479.9 Staged surgical approach to palliation of the patient with a single-ventricle circulation. **A,** Bidirectional Glenn shunt. The superior vena cava (SVC) is divided and detached from the right atrium (RA) and anastomosed end-to-side to the pulmonary artery, which has also been divided and detached from the right ventricle. **B,** Lateral tunnel Fontan. Inferior vena caval flow is directed upward through a synthetic or pericardial baffle sutured to the RA wall. The lower portion of the SVC (previously divided during the Glenn shunt) is now sutured directly to the right pulmonary artery. Thus blood flows from the upper body via the SVC directly into the lungs via the previous Glenn shunt and from the lower body via the baffle, through the RA but not emptying into the RA, directly into the lungs. The only remaining blood flow entering into the RA is from the coronary sinus, which represents the small amount of venous return coming directly from the left ventricle. The RA is thus excluded from the Fontan circuit. **C,** Extracardiac Fontan. The inferior vena cava (IVC) is detached from the RA, and an extracardiac synthetic conduit or homograft is used to direct that flow, outside the heart, to the inferior aspect of the right pulmonary artery (RPA). Both Fontan approaches achieve the same endpoint in isolating the venous circulation (blue blood) from the arterial circulation (red blood). The external conduit Fontan procedure is more common today because of concerns about atrial arrhythmias and/or blood clots related to the baffle in the RA. Many surgeons orient the connection from the IVC more centrally on the pulmonary arteries than shown in (**C**) to avoid a "collision" of flow from the upper and lower bodies, which in flow dynamic modeling studies has been shown to reduce the efficiency of the Fontan circulation, especially during exercise. *(Adapted from Burchill LJ, Wald RM, Mertens L. Single ventricles: echocardiographic assessment after the Fontan operation. In Otto CM, ed. The Practice of Clinical Echocardiography, 5th ed. Philadelphia: Elsevier; 2017, Figs. 49-6, 8, and 9.)*

are at increased risk, and if a pacemaker is required in these patients, dual-chamber pacing is the preferred approach.

Postoperative problems after the Fontan procedure are most often related to the increase in central venous pressure that occurs when the vena cavae are connected directly to the pulmonary arteries. Normal central venous pressure is 0-5 mm Hg, whereas after the Fontan operation, central venous pressure can rise to 10-15 mm Hg, and occasionally even more. In the immediate postoperative period, this elevation of systemic venous pressure can lead to fluid retention and pleural or pericardial effusions. The occurrence of these effusions has been markedly reduced with the cavopulmonary isolation procedure now in use, although prolonged chest tube drainage can still occur, but eventually resolves. Some centers use a fenestration at the time of the Fontan, consisting of a small communication between the inferior vena cava and the pulmonary artery conduit and the left atrium. This serves as a "pop-off" during early postoperative recovery and may hasten hospital discharge. The fenestration will result in some amount of right-to-left shunting and is therefore usually closed with a catheter closure device after the immediate postoperative period.

Late complications of the Fontan procedure include stenosis of the superior or inferior vena cava anastomosis, vena cava or pulmonary artery thromboembolism, protein-losing enteropathy, plastic bronchitis, renal dysfunction, immune deficiency, supraventricular arrhythmias (atrial flutter, paroxysmal atrial tachycardia), and hepatic injury, referred to as **Fontan-associated liver disease (FALD)**, as a result of persistently elevated central venous pressures. Rarely liver disease may predispose to the development of hepatocellular carcinoma. As more patients survive into young and middle adult years, the occurrence of these complications increases, and these patients require careful follow-up in a center skilled at caring for **adults with congenital heart disease (ACHDs)**. Oral budesonide or sildenafil has been used with varying success to treat protein-losing enteropathy associated with the Fontan procedure. MRI lymphangiography followed by thoracic duct ligation, decompression, or embolization is used to treat plastic bronchitis and other complications of a Fontan procedure. LV dysfunction may be a late occurrence, usually not until adolescence or young adulthood. Heart transplantation is a successful treatment option for pediatric patients with "failed" Fontan circuits but is a somewhat riskier procedure when performed in older adults. Patients with combined heart failure and liver dysfunction have been treated with combined heart-liver transplantation with good result.

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479.5 Double-Outlet Right Ventricle

Daniel Bernstein

Double-outlet right ventricle **(DORV)** is characterized when both the aorta and pulmonary artery arise from the right ventricle. The only outlet from the left ventricle occurs through a VSD emptying into the right ventricle, although some degree of override of the septum may place either the aorta or pulmonary artery partially over the left ventricle. Normally, the aortic and mitral valves are in fibrous continuity; in DORV the aortic and mitral valves are separated by a smooth muscular **conus**, like that seen under the normal pulmonary valve. In DORV the great arteries may be *normally related,* with the aorta closer to (or slightly overriding) the VSD, or the great arteries may be *malposed,* with the pulmonary artery closer to (or slightly overriding) the VSD. The degree to which the great artery closest to the VSD may override the defect is variable but must be at least 50% committed to the right ventricle to be termed DORV. When the VSD is subaortic, the defect may be viewed as part of a continuum with the **tetralogy of Fallot**, and the physiology, history, physical examination, ECG, and radiography depend on the degree of pulmonary stenosis, like the situation in tetralogy of Fallot (see Chapter 479.1). If the VSD is subpulmonic, there may be subvalvar, valvar, or supravalvar aortic stenosis, and

coarctation is a possibility as well. This is known as the **Taussig-Bing malformation**. The clinical presentation of these patients will depend on the degree of aortic obstruction, but because the pulmonary artery is usually wide open, the presentation will usually include some degree of pulmonary overcirculation and heart failure. If the aortic obstruction is severe or there is a coarctation, poor pulses, hypoperfusion, and cardiovascular collapse are possible presenting signs, especially when the PDA begins to close.

The 2D echocardiogram demonstrates both great vessels arising from the right ventricle and mitral-aortic valve discontinuity. The relationships between the aorta and pulmonary artery to the VSD can be delineated, and the presence of either pulmonary obstruction or aortic obstruction can be evaluated. The aortic arch is imaged to evaluate for coarctation. Cardiac catheterization is not necessarily required if the echocardiogram is straightforward. Angiography will show that the aortic and pulmonary valves lie in the same horizontal plane and that both arise predominantly or exclusively from the right ventricle.

Surgical correction depends on the relationship of the great vessels to the VSD. If the VSD is *subaortic,* the repair will be like that used for tetralogy of Fallot with patch closure of the VSD so that the left ventricle ejects blood into the aorta. In cases where the aorta is more distant from the left ventricle, repair may consist of creating an intraventricular tunnel so that the left ventricle ejects blood through the VSD, into the tunnel, and into the aorta. The pulmonary obstruction is relieved either with an outflow patch or with a right ventricle–to–pulmonary artery homograft conduit **(Rastelli operation)**. If the VSD is *subpulmonic,* the great vessels can be switched (see Chapter 479.6) and the Rastelli operation performed. However, if there is substantial aortic obstruction or if one of the ventricles is hypoplastic, a Norwood-style single-ventricle repair may be necessary (see Chapter 480.10). In selected small infants, palliation with an aortopulmonary shunt can provide symptomatic improvement and allow for adequate growth before corrective surgery is performed.

479.6 Transposition of the Great Arteries with Ventricular Septal Defect and Pulmonary Stenosis

Daniel Bernstein

The combination of TGA with VSD and pulmonary stenosis may mimic tetralogy of Fallot in its clinical features (see Chapter 479.1). However, because of the transposed great vessels, the site of obstruction is in the left as opposed to the right ventricle. The obstruction can be either valvular or subvalvular; the latter type may be *dynamic,* related to the interventricular septum or atrioventricular valve tissue, or *acquired,* as in patients with transposition and VSD after pulmonary arterial banding.

The age at which clinical manifestations initially appear varies from soon after birth to later infancy, depending on the degree of pulmonic stenosis. Clinical findings include cyanosis, decreased exercise tolerance, and poor physical development, like those described for tetralogy of Fallot; the heart is usually more enlarged. The pulmonary vasculature as seen on radiograph depends on the degree of pulmonary obstruction. The ECG usually shows right-axis deviation, right and left ventricular hypertrophy, and sometimes tall, spiked P waves. Echocardiography confirms the diagnosis and is useful in sequential evaluation of the degree and progression of the LV outflow tract obstruction. Cardiac catheterization, if necessary, shows that pulmonary arterial pressure is low and that oxygen saturation in the pulmonary artery exceeds that in the aorta, since pulmonary blood flow is coming directly from the left ventricle. Selective right and left ventriculography demonstrates the origin of the aorta from the right ventricle, the origin of the pulmonary artery from the left ventricle, the VSD, and the site and severity of the pulmonary stenosis.

An infusion of PGE_1 (0.05-0.1 μg/kg/min) should be started in neonates who present with cyanosis. When necessary, **balloon atrial septostomy** is performed to improve atrial-level mixing and to decompress the left atrium (see Chapter 480.2). Cyanotic infants may be palliated with an aortopulmonary shunt (see Chapter 479.1), followed by a Rastelli operation when older, as the preferred corrective procedure. The Rastelli procedure achieves physiologic and anatomic correction by (1) closure of the VSD using an intraventricular tunnel so that LV blood flow is directed to the aorta and (2) connection of the right ventricle to the distal pulmonary artery by an extracardiac homograft conduit (Fig. 479.10). These conduits will eventually become stenotic with patient growth and require replacement. Patients with milder degrees of pulmonary stenosis amenable to simple valvotomy may be able to undergo complete correction with an **arterial switch procedure** (see Chapter 480.2) and closure of the VSD. Surgical correction by the **Mustard or Senning operation** (see Chapter 480.2) with simultaneous closure of the VSD and relief of LV outflow obstruction may be an alternative when the position of the VSD is not suitable for a Rastelli operation; however, this procedure leaves the right ventricle as the systemic pumping chamber and has fallen out of favor.

479.7 Ebstein Anomaly of the Tricuspid Valve

Daniel Bernstein

Ebstein anomaly consists of downward displacement of an abnormal tricuspid valve into the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the RV myocardium (see Chapter 469). The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are adherent to the wall of the right ventricle. The right ventricle is thus divided into two parts by the abnormal tricuspid valve: the first, a thin-walled "atrialized" portion, is continuous with the cavity of the right atrium; the second, often smaller, portion consists of normal ventricular myocardium. The right atrium is enlarged as a result of tricuspid valve regurgitation, although the degree is extremely variable. In more severe forms of Ebstein anomaly, the effective output from the right side of the heart is decreased because of a combination of the poorly functioning small right ventricle, tricuspid valve regurgitation, and RVOT obstruction produced by the large, sail-like, anterior tricuspid valve leaflet. The severity of tricuspid valve displacement has been grouped into four degrees (A through D), known as the *Carpentier classification.* In newborns, RV function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing "functional" pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated ASD) to the left atrium and produces cyanosis (Fig. 479.11).

CLINICAL MANIFESTATIONS

The severity of symptoms and the degree of cyanosis are highly variable and depend on the extent of displacement of the tricuspid valve and the severity of RVOT obstruction. In many patients with milder forms of tricuspid valve displacement, symptoms are mild and may be delayed until the teenage years or young adult life; the patient may initially have fatigue, exercise intolerance, or palpitations as a result of cardiac dysrhythmias. The atrial right-to-left shunt is responsible for cyanosis, which may only be evident during exercise and, if long-standing, polycythemia. Jugular venous pulsations, an index of central venous pressure, may be normal or increased in those with tricuspid insufficiency. On palpation, the precordium is quiet. A holosystolic murmur caused by tricuspid regurgitation is audible over most of the anterior left side of the chest. A gallop rhythm is common and often associated with multiple clicks at the lower-left sternal border. A scratchy diastolic murmur may also be heard at the left sternal border. This murmur may mimic a pericardial friction rub.

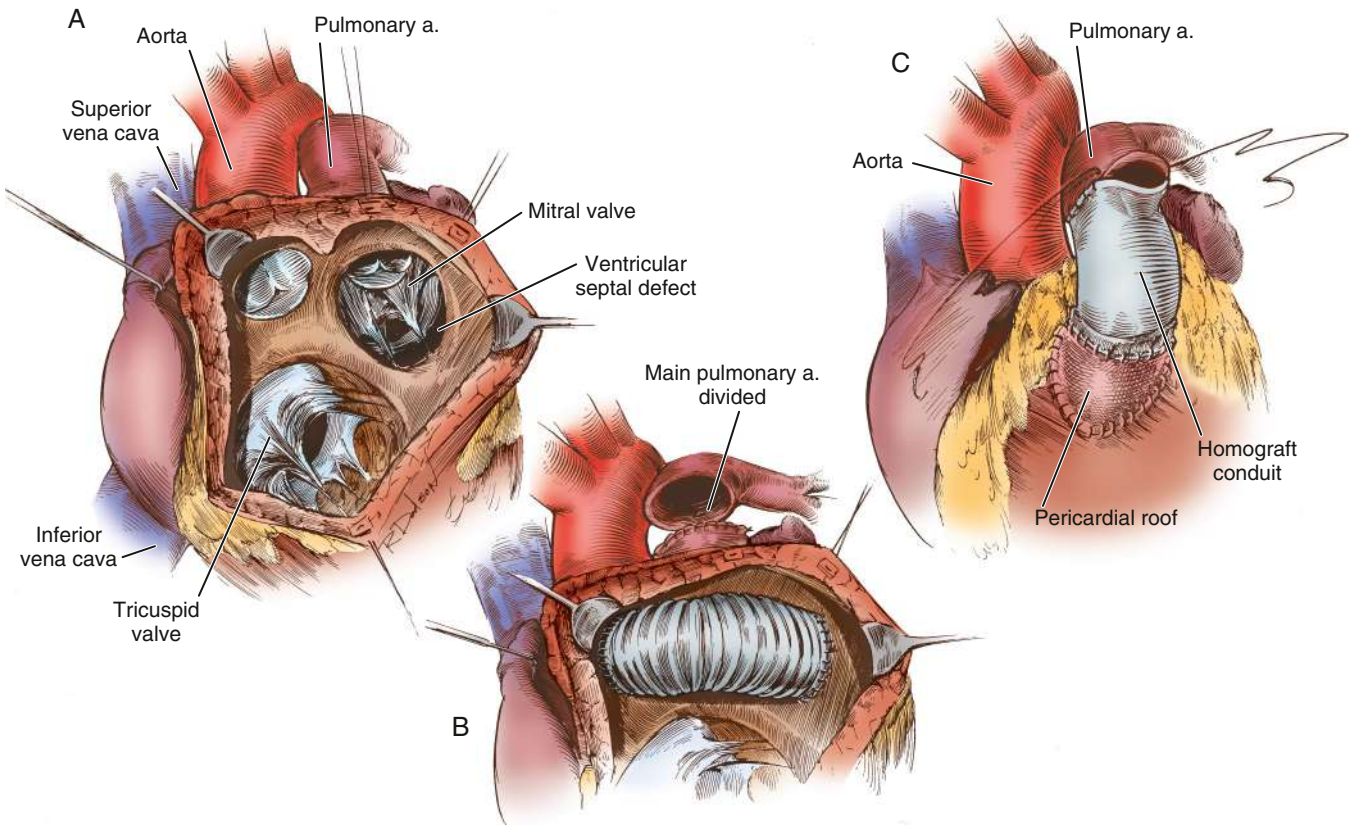

Fig. 479.10 A, Taussig-Bing type of double-outlet right ventricle with subpulmonary stenosis necessitating repair by the Rastelli technique. B, The main pulmonary artery is divided and oversewn proximally. The pulmonary valve lies within the baffle pathway. C, Completion of the Rastelli repair with a right ventricle–pulmonary artery allograft conduit. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al. Single-ventricle tricuspid atresia. In: Castañeda AR, Jonas RA. Mayer JE Jr, Hanley FL, eds. Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

Newborns with severe forms of Ebstein anomaly have marked cyanosis, massive cardiomegaly, and long holosystolic murmurs. Death may result from cardiac failure, hypoxemia, and pulmonary hypoplasia, the result of severe long-standing intrauterine right atrial enlargement. Spontaneous improvement may occur in some neonates as pulmonary vascular resistance falls and improves the ability of the right ventricle to provide pulmonary blood flow. The majority are dependent on a PDA, and thus on a prostaglandin infusion, for pulmonary blood flow. Fetuses diagnosed with Ebstein anomaly on fetal ultrasound can be particularly challenging. Severe leakage of the tricuspid valve is one of the few congenital heart lesions that cannot be bypassed by the parallel fetal circulation (see Chapter 470), and thus cardiac enlargement and fetal heart failure may supervene. When the heart enlarges, particularly the right atrium, compression of the lungs can result and the fetus is at risk for development of pulmonary hypoplasia.

DIAGNOSIS

The ECG usually shows a right bundle branch block without increased right precordial voltage, normal or tall and broad P waves, and a normal or prolonged P-R interval. **Wolff-Parkinson-White syndrome** may be present, and these patients may have episodes of supraventricular tachycardia (see Chapter 484). On radiographic examination, heart size varies from slightly enlarged to massive, box-shaped cardiomegaly caused by enlargement of the right atrium. *In newborns with severe Ebstein anomaly, the heart may be so enlarged as to totally obscure the pulmonary fields* (Fig. 479.12). Echocardiography is diagnostic and shows the degree of displacement of the tricuspid valve leaflets, a dilated right atrium, and any RVOT obstruction (Fig. 479.13). Pulsed and color Doppler examination demonstrates the degree of tricuspid regurgitation. In severe cases the pulmonary valve may appear immobile, and pulmonary blood flow may come solely from the ductus arteriosus. It may be difficult to distinguish true from functional pulmonary valve atresia. Cardiac catheterization, which is not usually necessary, confirms the presence of a large right atrium, an abnormal tricuspid valve, and any right-to-left shunt at the atrial level. The risk of arrhythmia is significant during catheterization and angiographic studies.

TREATMENT

Neonates with milder degrees of cyanosis can sometimes be managed medically, waiting to see how they do once their pulmonary vascular resistance decreases over the first few weeks of life. Those with moderate to severe hypoxia are initially treated with prostaglandins, mechanical ventilation and inhaled nitric oxide in an attempt to enhance pulmonary blood flow by reducing pulmonary vascular resistance. Surgical options for these patients include an aortopulmonary (Blalock-Taussig) shunt, tricuspid valve replacement (most often with a bioprosthetic valve), or surgical repair of the tricuspid valve (cone procedure). In the critically ill neonate, closure of the valve (creating tricuspid atresia physiology) with an aortopulmonary shunt (Starnes procedure), with eventual single-ventricle repair using the Fontan palliation (see Chapter 479.4) is

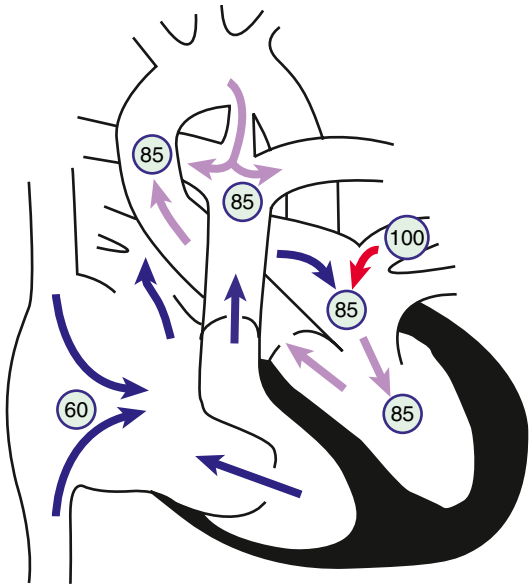

Fig. 479.11 Physiology of Ebstein anomaly of the tricuspid valve. *Circled numbers* represent oxygen saturation values. Inferior displacement of the tricuspid valve leaflets into the right ventricle has resulted in a thin-walled, low-pressure "atrialized" segment of right ventricle. The tricuspid valve is grossly insufficient. Right atrial blood flow is shunted right to left across an atrial septal defect or patent foramen ovale into the left atrium. Some blood may cross the right ventricular outflow tract and enter the pulmonary artery; however, in severe cases, the right ventricle may generate insufficient force to open the pulmonary valve, and "functional pulmonary atresia" results. In the left atrium, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected via the aorta. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). Severe cyanosis will develop in neonates with a severe Ebstein anomaly when the PDA closes.

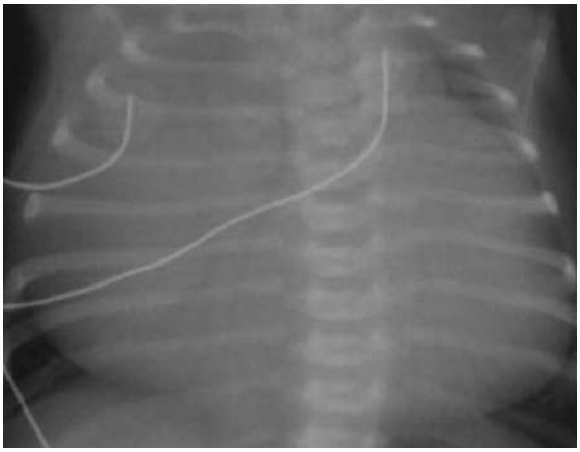

Fig. 479.12 Massive cardiomegaly in a newborn infant with severe Ebstein anomaly. The heart is so enlarged (in part because of a massive right atrium) that lung hypoplasia is a major concern.

an option. Many infants with Ebstein anomaly who have undergone valve repair will also have a bidirectional Glenn shunt performed to reduce the volume load on the right ventricle and reduce the amount of tricuspid regurgitation (see Chapter 479.4). In older children with mild or moderate disease, control of supraventricular dysrhythmias (medications or radiofrequency ablation), if present,

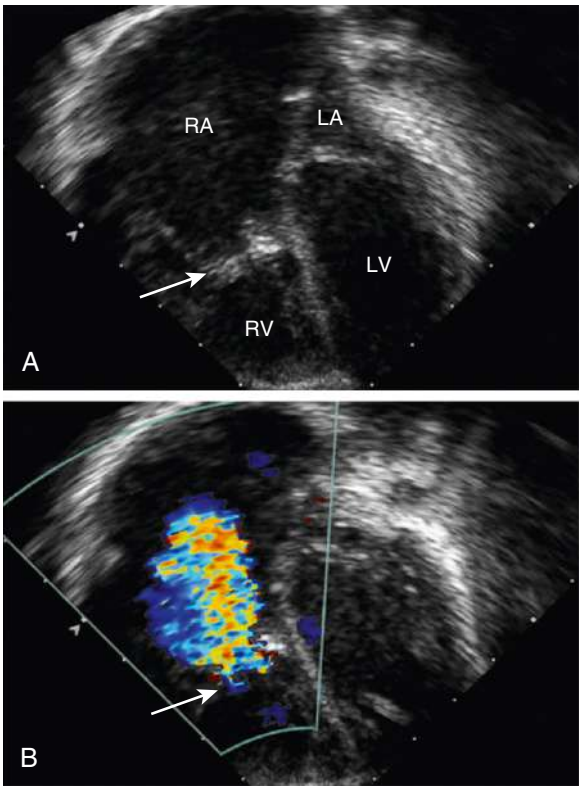

Fig. 479.13 Echocardiographic demonstration of Ebstein anomaly of the tricuspid valve. **A,** Subcostal, four-chamber, 2D view showing severe displacement of the tricuspid valve leaflets *(arrow)* inferiorly into the right ventricle. The location of the tricuspid valve annulus is outlined by the arrow. The portion of the right ventricle between the valve annulus and the valve leaflets is the "atrialized" component. **B,** Color Doppler examination showing severe regurgitation of the dysplastic tricuspid valve. Note that the regurgitant turbulent flow *(arrow)* begins halfway into the right ventricular chamber, at the location of the displaced valve leaflets. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

is of primary importance; surgical treatment may not be necessary until adolescence or young adulthood. Older patients with severe tricuspid regurgitation can undergo repair or replacement of the abnormal tricuspid valve along with closure of the ASD. In some patients, a bidirectional Glenn shunt is also performed, with the superior vena cava anastomosed to the pulmonary arteries. This procedure reduces the volume of blood that the dysfunctional right side of the heart has to pump, thus creating a "one-and-one-half ventricle repair."

PROGNOSIS AND COMPLICATIONS

The prognosis in Ebstein anomaly is extremely variable and depends on the severity of the defect. The prognosis is more guarded for neonates or infants with cyanosis. Patients with milder degrees of Ebstein anomaly usually survive well into adult life. An associated form of left ventricular cardiomyopathy, **isolated left ventricular noncompaction (LVNC)**, is seen in up to 18% of patients with Ebstein anomaly, and the severity of the LV dysfunction directly affects the prognosis.

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Chapter 480

Cyanotic Congenital Heart Disease: Lesions Associated with Increased Pulmonary Blood Flow

480.1 d-Transposition of the Great Arteries

Daniel Bernstein

d-Transposition of the great arteries or vessels (d-TGA or d-TGV) accounts for approximately 5% of all congenital heart disease. In this anomaly, the systemic veins return, as normal, to the right atrium and the pulmonary veins return to the left atrium. The connections between the atria and ventricles are also normal (i.e., **atrioventricular concordance**). The aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Fig. 480.1). In normally related great vessels (i.e., in the normal heart) the aorta is posterior and to the right of the pulmonary artery. Whereas in d-TGA the aorta is anterior and to the right of the pulmonary artery (the *d* indicates a dextropositioned aorta, *transposition* indicates that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle). Desaturated blood returning from the body to the right side of the heart goes inappropriately out via the aorta and back to the body again, whereas oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs. Thus the systemic and pulmonary circulations exist as two parallel circuits. Survival in the immediate newborn period is provided by the foramen ovale and the ductus arteriosus, which permit some mixture of oxygenated and deoxygenated blood. Approximately 50% of patients with d-TGA also have a ventricular septal defect (VSD), which usually provides for better mixing. The clinical findings and hemodynamics vary in relation to the presence or absence of associated defects (e.g., VSD or pulmonary stenosis). d-TGA is more common in infants of diabetic mothers and in males (a ratio of 3:1). When accompanied by other cardiac defects such as pulmonic stenosis or right aortic arch, d-TGA can be associated with deletion of chromosome 22q11.2 (**DiGeorge syndrome**; see Chapter 473).

480.2 d-Transposition of the Great Arteries with Intact Ventricular Septum

Daniel Bernstein

d-TGA with an intact ventricular septum is also referred to as **simple TGA** or **isolated TGA**. Before birth, oxygenation in the upper and lower body fetal circulation is only slightly abnormal, given that oxygenated blood enters the heart from the placenta, umbilical vein, and inferior vena cava. After birth, once the ductus arteriosus begins to close, the minimal mixing of systemic and pulmonary blood by the patent foramen ovale is usually insufficient and severe hypoxemia ensues, generally within the first few days of life.

CLINICAL MANIFESTATIONS

Cyanosis and tachypnea are most often recognized within the first hours or days of postnatal life. Untreated, most of these infants would not survive the neonatal period. Hypoxemia is usually moderate to severe, depending on the degree of atrial-level shunting and whether the ductus is partially open or totally closed. This condition is a medical emergency, and only early diagnosis and appropriate intervention can avert the development of prolonged severe hypoxemia and acidosis, which lead to death. Physical findings, other than cyanosis, may be remarkably nonspecific. The precordial impulse may be normal, or a parasternal heave may be present. The second heart sound (S_2) is usually single and loud, although it may be split. Murmurs may be absent, or a soft systolic ejection murmur may be noted at the mid-left sternal border.

DIAGNOSIS

The electrocardiogram (ECG) is usually normal, showing the expected neonatal right-sided dominant pattern. Chest radiographs may show mild cardiomegaly and a narrow mediastinum (the classic "egg-shaped heart"). In the early newborn period, the pulmonary blood flow is generally normal. As pulmonary vascular resistance (PVR) drops during the first several weeks of postnatal life, evidence of increased pulmonary blood flow becomes apparent. Arterial blood partial pressure of oxygen (Pao_2) is low and does not rise appreciably after the patient breathes 100% oxygen (hyperoxia test), although this test may not be totally reliable. Echocardiography is diagnostic and confirms the transposed ventricular-arterial connections (Fig. 480.2). The size of the interatrial communication and the ductus arteriosus can be visualized and the degree of mixing assessed by pulsed and color Doppler examination. The presence of any associated lesion, such as left ventricular outflow tract obstruction or a VSD, can also be assessed. The origins of the coronary arteries can be imaged, although echocardiography is not as accurate as catheterization for

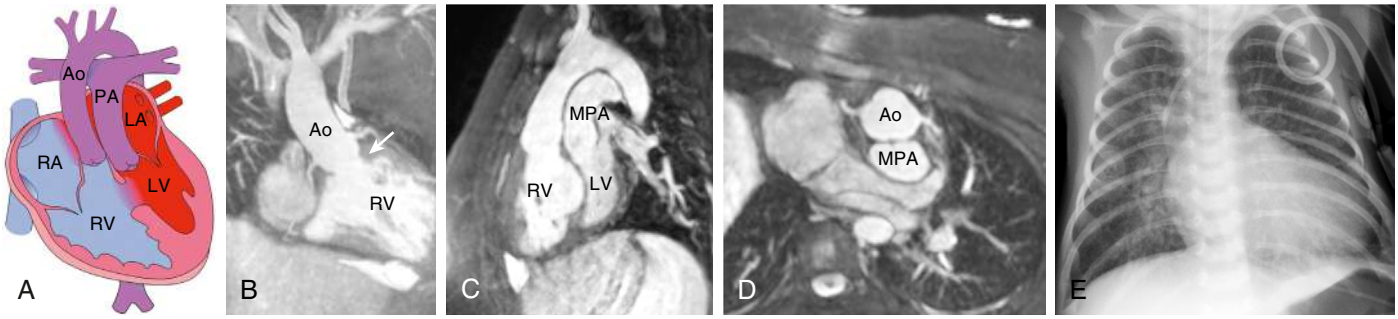

Fig. 480.1 d-Looped transposition of the great arteries (TGA). **A,** Diagram of d-TGA, with the main pulmonary artery (MPA) arising from the left ventricle (LV) and the aorta (Ao) arising from the right ventricle (RV). The degree of cyanosis is variable and depends on the presence of intracardiac shunts such as an atrial septal defect or a ventricular septal defect (VSD) to get oxygenated blood into the systemic circulation. LA, Left atrium; PA, pulmonary artery; RA, right atrium. **B** and **C,** Oblique reformatted images from a 3D steady-state free-precession sequence show (**B**) the Ao arising from the anterior RV with a subaortic conus *(arrow),* and (**C**) the MPA arising from the posterior LV. **D,** The Ao and MPA have a parallel "back-to-front" arrangement. **E,** This parallel back-to-front arrangement contributes to the narrow mediastinum and "egg on a string" appearance seen on chest radiography. This patient has a large VSD with increased pulmonary blood flow. *(From Frost JL, Krishnamurthy R, Sena L. Cardiac imaging. In: Walters MM, Robertson RL, eds. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier; 2017, Fig 3-20, p. 75.)*

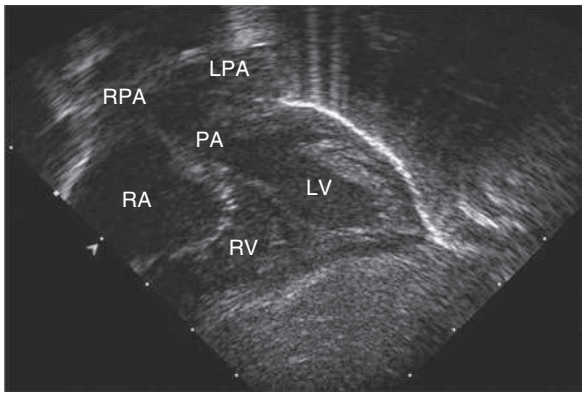

Fig. 480.2 Subcostal four-chamber 2D echocardiographic demonstration of d-transposition of the great arteries. The pulmonary artery (PA) can be seen arising directly from the left ventricle (LV). The immediate bifurcation of this great vessel into the branch pulmonary arteries differentiates it from the aorta, which branches more distally from the heart. LPA, Left pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

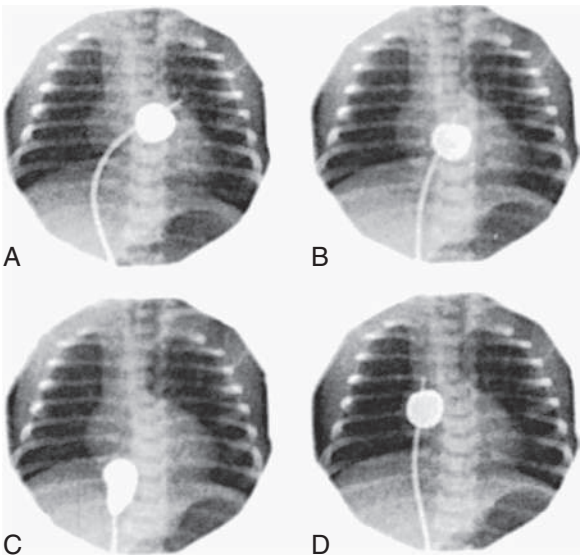

Fig. 480.3 Rashkind balloon atrial septostomy. Four frames from a continuous cineangiogram show the creation of an atrial septal defect in a hypoxemic newborn infant with transposition of the great arteries and an intact ventricular septum. **A**, Balloon inflated in the left atrium. **B**, The catheter is jerked suddenly so that the balloon ruptures the foramen ovale. **C**, Balloon in the inferior vena cava. **D**, Catheter advanced to the right atrium to deflate the balloon. The time from **A** to **C** is <1 sec.

this purpose. Cardiac catheterization may be performed in patients for whom noninvasive imaging is diagnostically inconclusive, where an unusual coronary artery anomaly is suspected, or in patients who require emergency **balloon atrial septostomy (i.e., the Rashkind procedure)**. Catheterization will show right ventricular pressure to be at a systemic level because this ventricle is supporting the systemic circulation. The blood in the left ventricle (LV) and pulmonary artery has a higher oxygen saturation than that in the aorta. Depending on the age at catheterization, LV and pulmonary artery pressure can vary from a systemic level to <50% of systemic-level pressure. Right ventriculography demonstrates the anterior and rightward aorta originating from the right ventricle (RV), as well as the intact ventricular septum. Left ventriculography shows that the pulmonary artery arises exclusively from the LV.

Anomalous coronary arteries are noted in 10–15% of patients and can be defined by an aortic root injection or by selective coronary arteriography.

TREATMENT

When transposition is suspected, an infusion of prostaglandin E_1 (PGE_1, 0.05-0.1 μg/kg/min) should be initiated immediately to maintain patency of the ductus arteriosus and improve oxygenation. Because of the risk of apnea associated with prostaglandin infusion, an individual skilled in neonatal endotracheal intubation should be available. Hypothermia intensifies the metabolic acidosis resulting from hypoxemia, and thus the patient should be kept warm. Prompt correction of acidosis and hypoglycemia is essential.

Infants who remain severely hypoxic or acidotic despite prostaglandin infusion should undergo **Rashkind balloon atrial septostomy** (Fig. 480.3). A Rashkind atrial septostomy is also usually performed in patients in whom any significant delay in surgery is expected. If surgery is planned during the first 2 weeks of life and the patient is stable, catheterization and atrial septostomy may often be avoided.

A successful Rashkind atrial septostomy should result in a rise in Pao_2 to 35-50 mm Hg and elimination of any pressure gradient across the atrial septum. Some patients with TGA and VSD (see Chapter 480.3) may require balloon atrial septostomy because of poor mixing, even though the VSD is large. Others may benefit from decompression of the left atrium to alleviate the symptoms of increased pulmonary blood flow and left-sided heart failure.

The **arterial switch (Jatene) procedure** is the surgical treatment of choice for neonates with d-TGA and an intact ventricular septum and is usually performed within the first 2 weeks of life. The reason for this time frame is that as PVR declines after birth, pressure in the LV (connected to the pulmonary vascular bed) also declines. This pressure drop results in a decrease in LV mass over the first few weeks of life. If the arterial switch operation is attempted after LV pressure (and mass) has declined too far, the LV will be unable to generate adequate pressure to pump blood to the high-pressure systemic circulation. The arterial switch operation involves dividing the aorta and pulmonary artery just above the sinuses and reanastomosing them in their correct anatomic positions. The coronary arteries are removed from the old aortic root along with a button of aortic wall and reimplanted in the old pulmonary root (now called the **neoaorta**). By using a button of great vessel tissue, the surgeon avoids having to suture directly onto the coronary artery (Fig. 480.4); this is the major innovation that has allowed the arterial switch to replace previous atrial switch operations for d-TGA. Rarely, a two-stage arterial switch procedure, with initial placement of a pulmonary artery band, may be used in patients presenting late who already have had a reduction in LV muscle mass and pressure. The arterial switch procedure has a survival rate of >95% for uncomplicated d-TGA. It restores the normal physiologic relationships of systemic and pulmonary arterial blood flow and eliminates the long-term complications of the previously used atrial switch procedure.

Previous operations for d-TGA consisted of some form of **atrial switch procedure** (**Mustard** or **Senning** operation). These procedures produced excellent early survival (85–90%) but had significant long-term morbidities. Atrial switch procedures reverse blood flow at the atrial level by creating an interatrial baffle that directs systemic venous blood returning from the venae cavae to the left atrium, where it will enter the LV, the pulmonary artery, and the lungs. The same baffle also permits oxygenated pulmonary venous blood to cross over to the right atrium, RV, and aorta. Atrial switch procedures involve significant atrial surgery and have been associated with the late development of atrial conduction disturbances, sick sinus syndrome with bradyarrhythmia and tachyarrhythmia, atrial flutter, sudden death, superior or inferior vena cava syndrome, edema, ascites, and protein-losing enteropathy. The atrial switch procedure also leaves the RV as the systemic pumping chamber, and this "systemic" RV often begins to fail in young adulthood. Atrial switch operations are currently reserved for patients whose anatomy is such that they are not candidates for the arterial switch procedure.

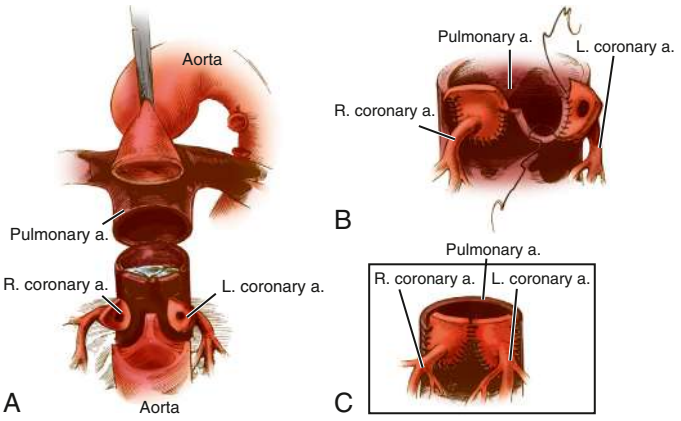

Fig. 480.4 Method for translocating the coronary arteries in the arterial switch (Jatene) procedure. **A,** The aorta (anterior) and the pulmonary artery (posterior) have been transected to allow visualization of the left and right coronary arteries. The coronaries have been excised from their respective sinuses, including a large flap (button) of arterial wall. Equivalent segments of the wall of the pulmonary artery (which will become the neoaorta) are also removed. **B,** The aortocoronary buttons are sutured into the proximal portion of the neoaorta. With this technique all sutures are placed in the button of aortic wall rather than directly on the coronary arteries. **C,** Completed anastomosis of the left and right coronary arteries to the neoaorta. *(Adapted from Castañeda AR, Jonas RA, Mayer JE Jr, et al. Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

480.3 Transposition of the Great Arteries with Ventricular Septal Defect

Daniel Bernstein

If the VSD associated with d-TGA is small, the clinical manifestations, laboratory findings, and treatment are similar to those described previously for transposition with an intact ventricular septum. A harsh systolic murmur is audible at the lower left sternal border, resulting from flow through the defect. Many of these small defects eventually close spontaneously and may not need to be addressed at the time of surgery.

When the VSD is large and not restrictive to ventricular ejection, significant mixing of oxygenated and deoxygenated blood usually occurs and clinical manifestations of cardiac failure are seen. The degree of cyanosis may be subtle and sometimes may not be recognized until an oxygen saturation measurement is performed. The murmur is holosystolic and generally indistinguishable from that produced by a large VSD in patients with normally related great arteries. The heart is usually significantly enlarged.

Cardiomegaly, a narrow mediastinal waist, and increased pulmonary vascularity are demonstrated on the chest radiograph. The ECG findings can be variable. It can show prominent P waves and isolated RV hypertrophy or biventricular hypertrophy. Occasionally, dominance of the LV is present. Usually, the QRS axis is to the right, but it can be normal or even to the left. The diagnosis is confirmed by echocardiography, and the extent of pulmonary blood flow can also be estimated by the degree of enlargement of the left atrium and ventricle. In equivocal cases, the diagnosis can be confirmed by cardiac catheterization. Right and left ventriculography indicate the presence of arterial transposition and demonstrate the site and size of the VSD. Systolic pressure is equal in the two ventricles, the aorta, and the pulmonary artery. Left atrial pressure may be much higher than right atrial pressure, a finding indicative of a restrictive communication at the atrial level. At the time of cardiac catheterization, Rashkind balloon atrial septostomy may be performed to decompress the left atrium, even when adequate mixing is occurring at the ventricular level.

Surgical treatment is advised soon after diagnosis because heart failure and failure to thrive are difficult to manage and pulmonary vascular disease can develop unusually rapidly in these patients. Preoperative management with diuretics and other anticongestive therapies (including elective intubation and positive pressure ventilation) stabilize the patient before surgery.

Patients with d-TGA and a VSD without pulmonic stenosis can be treated with an arterial switch procedure combined with VSD closure. In these patients, the arterial switch operation can be safely performed after the first 2 weeks of life because the VSD results in equal pressure in both ventricles and prevents regression of LV muscle mass. At major centers, however, there is no reason to delay repair, as results are excellent when the surgery is performed in the neonatal period.

480.4 l-Transposition of the Great Arteries (Corrected Transposition)

Daniel Bernstein

In l-transposition of the great arteries (l-TGA), both the atrioventricular and the ventriculoarterial relationships are discordant: the right atrium is connected to an LV and the left atrium to an RV, which is also known as **ventricular inversion**. The great arteries are also transposed, with the aorta arising from the RV and the pulmonary artery from the LV. In contrast to d-TGA, the aorta arises to the left of the pulmonary artery (thus the designation *l* for levo-transposition). The aorta may be anterior to the pulmonary artery, although often they are nearly side by side.

The physiology of l-TGA is quite different from that of d-TGA. Desaturated systemic venous blood returns via the vena cavae to a normal right atrium, from which it passes through a bicuspid atrioventricular (mitral) valve into a right-sided ventricle that has the architecture and smooth wall morphologic features of the normal LV (Fig. 480.5). Because transposition is also present, however, the desaturated blood ejected from this LV enters the transposed pulmonary artery and flows into the lungs, as it would in the normal circulation. Oxygenated pulmonary venous blood returns to a normal left atrium, passes through a tricuspid atrioventricular valve into a left-sided ventricle, which has the trabeculated morphologic features of a normal RV, and is then ejected into the transposed aorta. The double inversion of the atrioventricular and ventriculoarterial relationships result in desaturated right atrial blood appropriately flowing to the lungs and oxygenated pulmonary venous blood appropriately flowing to the aorta. The circulation is thus physiologically "corrected." Without other defects, the hemodynamics would be almost normal. In most patients, however, associated anomalies coexist: VSD, Ebstein-like abnormalities of the left-sided atrioventricular (tricuspid) valve, pulmonary valvular or subvalvular stenosis (or both), and atrioventricular conduction disturbances (complete heart block, accessory pathways such as Wolff-Parkinson-White syndrome).

CLINICAL MANIFESTATIONS

Symptoms and signs are widely variable and are usually determined by the associated lesions. If there is a VSD and pulmonary outflow is unobstructed, the clinical signs are similar to those of an isolated VSD. If l-TGA is associated with pulmonary stenosis and a VSD, the clinical signs are more similar to those of tetralogy of Fallot.

DIAGNOSIS

The chest radiograph may suggest the abnormal position of the great arteries; the ascending aorta occupies the upper left border of the cardiac silhouette and has a straight profile. The ECG, in addition to any atrioventricular conduction disturbances, may show abnormal P waves; absent Q waves in V_6; abnormal Q waves in leads III, aVR, aVF, and V_1; and upright T waves across the precordium. The echocardiogram is diagnostic. The characteristic echocardiographic features of the RV (moderator band, coarser trabeculations, tricuspid valve that sits more inferiorly compared with the bicuspid mitral valve, and a smooth muscular conus or infundibulum separating the atrioventricular valve

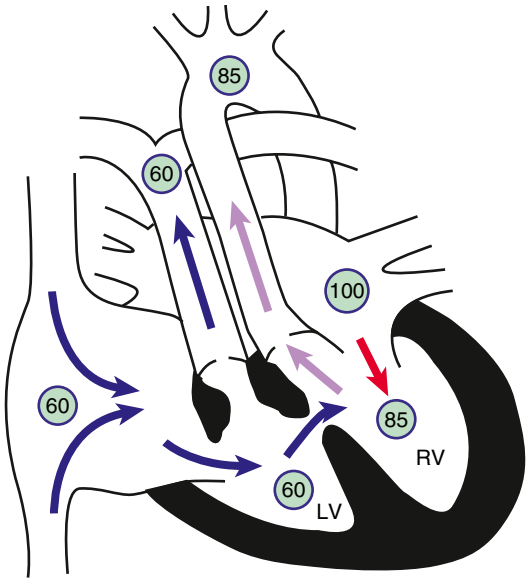

Fig. 480.5 Physiology of l-transposition or corrected transposition of the great arteries (l-TGA) with a ventricular septal defect and pulmonic stenosis (VSD + PS). *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Blood from the right atrium flows through the mitral valve into the "inverted" left ventricle (LV). The left ventricle is, however, attached to the transposed pulmonary artery. Therefore despite the anomalies, desaturated blood still winds up in the pulmonary circulation. Saturated blood returns to the left atrium, traverses the tricuspid valve into the "inverted" right ventricle (RV), and is pumped into the transposed aorta. This circulation would be totally "corrected" were it not for the frequent association of other congenital anomalies, in this case, VSD + PS. Because of the stenotic pulmonary valve, some left ventricular blood flow crosses the VSD and into the right ventricle and the ascending aorta, and systemic desaturation results.

from the semilunar valve) allow the echocardiographer to determine the presence of **atrioventricular discordance** (right atrium connected to LV; left atrium to RV) and ventriculoarterial discordance (RV connected to aorta; LV to pulmonary artery).

Surgical treatment of the associated anomalies, most often the VSD, is complicated by the position of the bundle of His, which can be injured at surgery and result in heart block. Identification of the usual course of the bundle in corrected transposition (running superior to the defect) has been accomplished by mapping the conduction system so that the surgeon can avoid the bundle of His during repair. Even without surgical injury, patients with l-TGA are at risk for developing heart block as they grow older.

Because simple surgical correction leaves the RV as the systemic pumping chamber, and thus vulnerable to late ventricular failure, surgeons have become more aggressive about trying operations that use the LV as the systemic pumping chamber. This is accomplished by performing an atrial switch operation (see Chapter 480.3) to reroute the systemic and pulmonary venous returns in combination with an arterial switch operation to reroute the ventricular outflows **(double switch procedure)**. The long-term benefit of this approach in preserving systemic ventricular function is still under investigation.

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480.5 Double-Outlet Right Ventricle Without Pulmonary Stenosis

Daniel Bernstein

In double-outlet RV without pulmonary stenosis, both the aorta and the pulmonary artery arise from the RV (see Chapter 479.5). The only outlet from the LV is through a VSD. In the absence of obstruction to pulmonary blood flow, clinical manifestations are similar to those of an uncomplicated VSD with a large left-to-right shunt, although mild systemic desaturation may result from mixing of oxygenated and deoxygenated blood in the RV. The ECG usually shows biventricular hypertrophy. Echocardiography is diagnostic and shows the right ventricular origin of both great arteries, their anteroposterior relationship, and the relationship of the VSD to each of the great arteries. Surgical correction is dependent on these relationships. If the VSD is subaortic, it is accomplished by creation of an intracardiac tunnel. Blood is then ejected from the LV via the VSD into the aorta. If the VSD is subpulmonic, an arterial switch may be performed in combination with an intracardiac tunnel. If pulmonary blood flow is excessive enough to cause congestive heart failure, pulmonary arterial banding may be required in infancy, followed by surgical correction when the child is bigger. When associated pulmonary stenosis is present, cyanosis is more marked, pulmonary blood flow is decreased, and clinical presentation may be similar to that of tetralogy of Fallot.

480.6 Double-Outlet Right Ventricle with Malposition of the Great Arteries (Taussig-Bing Anomaly)

Daniel Bernstein

In double-outlet RV with malposed great arteries, the VSD is usually directly subpulmonic and the aorta distant from the LV. Sometimes both the pulmonary and the aortic valve may be located close to the VSD (**doubly committed** VSD) and sometimes neither is (**doubly uncommitted** VSD). The term *malposition* is used instead of *transposition* because both great arteries arise from the RV. Aortic obstructive lesions are common, including valvular and subvalvular aortic stenosis, coarctation of the aorta, and interruption of the aortic arch. Because pulmonary blood flow is unobstructed, patients experience cardiac failure early in infancy and are at risk for the development of pulmonary vascular disease and cyanosis. If aortic obstructive lesions are a component, patients can present with poor systemic output and cardiovascular collapse, particularly after the ductus arteriosus begins to close. Cardiomegaly is usual, and a parasternal systolic ejection murmur is audible, sometimes preceded by an ejection click and loud closure of the pulmonary valve. The ECG shows right axis deviation and right, left, or biventricular hypertrophy. The chest radiograph shows cardiomegaly and prominence of the pulmonary vasculature. The anatomic features of the anomaly and associated abnormalities are usually demonstrated by echocardiography, augmented if necessary by either cardiac catheterization, MRI, or CT. Palliation may be achieved by corrective surgery or pulmonary arterial banding in early infancy and surgical correction at a later age, which may be accomplished by an arterial switch procedure (see Chapter 480.2) combined with an intracardiac baffle or some modification of the Rastelli procedure (see Chapter 479.5).

480.7 Total Anomalous Pulmonary Venous Return

Daniel Bernstein

Abnormal development of the pulmonary veins may result in either partial or complete anomalous drainage into the systemic venous circulation. Partial anomalous pulmonary venous return (PAPVR) is usually an acyanotic lesion (see Chapter 475.4). Total anomalous pulmonary venous return (TAPVR) is associated with total mixing of systemic venous and pulmonary venous blood flow within the heart and thus produces cyanosis.

In TAPVR, there is no direct pulmonary venous connection into the left atrium (Fig. 480.6). The pulmonary veins may drain **above** the diaphragm: into the right atrium directly, into the coronary sinus, or into the superior vena cava by a "vertical vein"; or they may drain **below** the

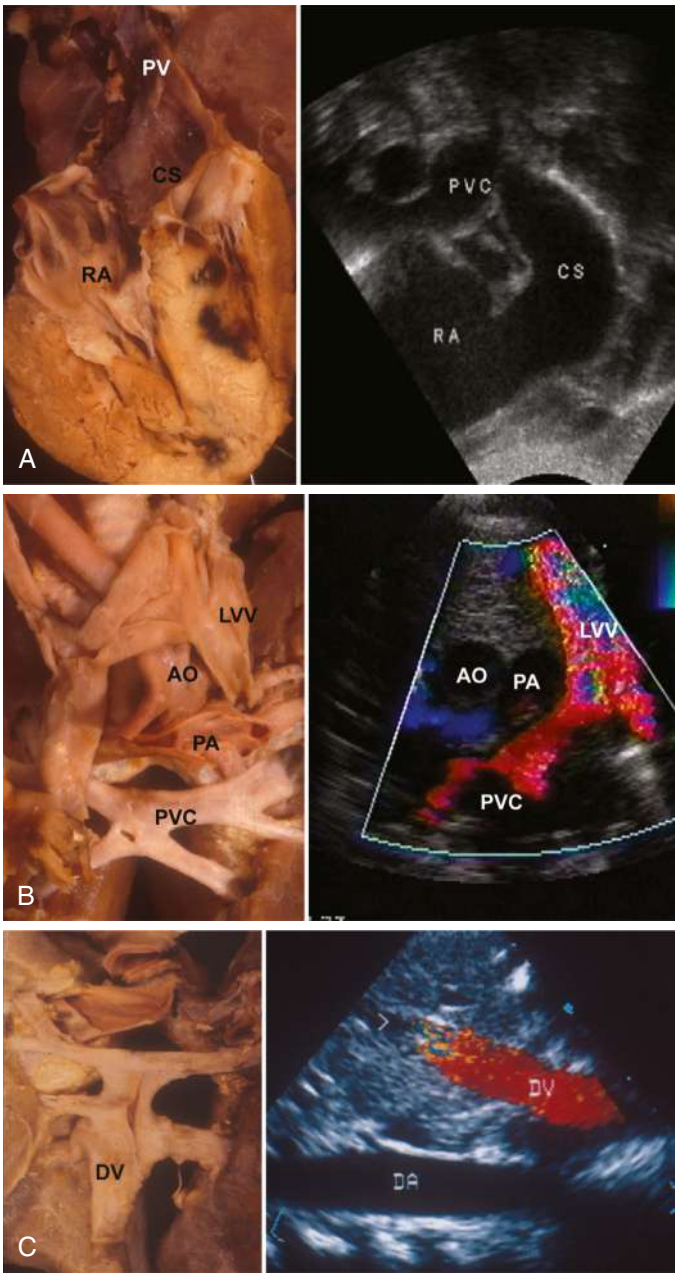

Fig. 480.6 A, Subcostal view demonstrating total anomalous pulmonary drainage to the coronary sinus. Note the dilated coronary sinus in both images. The echocardiogram also demonstrates an associated confluence that connects to the coronary sinus. B, Suprasternal view demonstrating total anomalous pulmonary venous drainage to a left vertical vein. Note the direction of flow in the vertical vein that differentiates it from a left superior vena cava. C, Total anomalous pulmonary venous drainage below the diaphragm. The specimen shows the pulmonary veins as they enter the confluence, whereas the echocardiogram demonstrates the descending veins as they enter the liver. Note that the direction of flow is away from the heart. AO, Aorta; CS, coronary sinus; DA, descending aorta; DV, descending vein; LVV, left vertical vein; PA, pulmonary artery; PV, pulmonary vein; PVC, pulmonary venous confluence; RA, right atrium. *(From Webb GD, Smallhorn, JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75-32, p. 1553.)*

diaphragm and join into a "descending vein" that enters the inferior vena cava or one of its major tributaries, often through the ductus venosus. This latter form of anomalous venous drainage is most often associated with *obstruction* to venous flow, usually as the ductus venosus closes soon after birth, although **supracardiac** anomalous veins may also become obstructed. Occasionally, the drainage may be **mixed**, with some veins draining above and others below the diaphragm.

Table 480.1 Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50)	
Left superior vena cava (40)	40
Right superior vena cava (10)	75
Cardiac (25)	
Coronary sinus (20)	10
Right atrium (5)	5
Infracardiac (20)	95–100
Mixed (5)	

All forms of TAPVR involve mixing of oxygenated and deoxygenated blood before or at the level of the right atrium **(total mixing lesion)**. This mixed right atrial blood either passes into the RV and pulmonary artery or passes through an atrial septal defect (ASD) or patent foramen ovale into the left atrium, which will be the only source of oxygenated systemic blood flow. The right atrium and ventricle and the pulmonary artery are generally enlarged, whereas the left atrium and ventricle may be normal or small. The clinical manifestations of TAPVR depend on the presence or absence of *obstruction* of the venous channels (Table 480.1). If pulmonary venous return is obstructed, severe pulmonary congestion and pulmonary hypertension develop; rapid deterioration occurs without surgical intervention. *Obstructed TAPVR is a pediatric cardiac surgical emergency because prostaglandin therapy is usually not effective.*

CLINICAL MANIFESTATIONS

Two major clinical patterns of TAPVR are seen, depending on the presence or absence of obstruction. Those neonates with severe obstruction to pulmonary venous return, most prevalent in the **infracardiac** group (see Table 480.1), present with severe cyanosis and respiratory distress. Murmurs may not be present. These infants are severely ill and fail to respond to mechanical ventilation. Rapid diagnosis and surgical correction are necessary for survival. In contrast, those with mild or no obstruction to pulmonary venous return are usually characterized by the development of heart failure as the PVR falls, with mild to moderate degrees of desaturation. Systolic murmurs may be audible along the left sternal border, and a gallop rhythm may be present. Some infants may have mild obstruction in the neonatal period and develop worsening obstruction as time passes.

DIAGNOSIS

The ECG demonstrates RV hypertrophy (usually a qR pattern in V_3R and V_1, and P waves are frequently tall and spiked). In neonates with marked pulmonary venous obstruction, the chest radiograph demonstrates a very dramatic perihilar pattern of pulmonary edema and a small heart (Fig. 480.7A). This appearance can sometimes be confused with primary pulmonary disease, and the differential diagnosis includes persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia, pulmonary lymphangiectasia, and other heart defects (hypoplastic left heart syndrome). In older children, if the anomalous pulmonary veins enter the innominate vein and persistent left superior vena cava (see Fig. 480.7B), a large supracardiac shadow can be seen, which together with the normal cardiac shadow forms a *snowman* appearance. In most cases without obstruction, the heart is enlarged, the pulmonary artery and RV are prominent, and pulmonary vascularity is increased.

The echocardiogram demonstrates a large RV and usually identifies the pattern of abnormal pulmonary venous connections

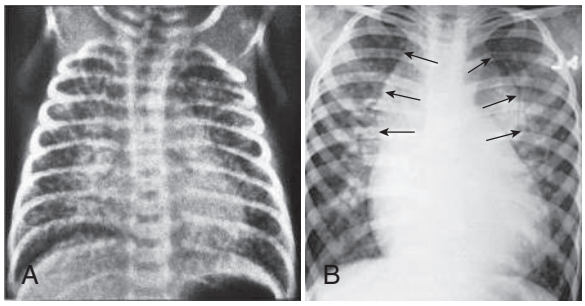

Fig. 480.7 Chest radiographs of total anomalous pulmonary venous return (TAPVR). **A,** A newborn with TAPVR to a descending vein (below the diaphragm) with obstruction, showing marked pulmonary venous congestion and normal heart size. **B,** TAPVR to the left superior vena cava (preoperative image). *Arrows* point to the supracardiac shadow, which produces the "snowman" or figure 8 configuration. Cardiomegaly and increased pulmonary vascularity are evident.

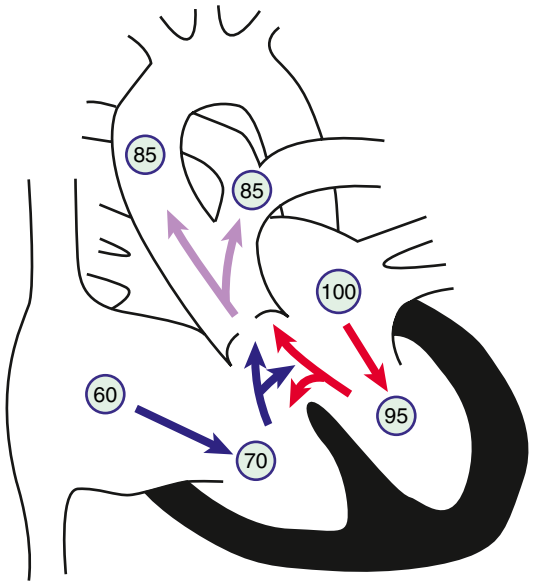

Fig. 480.8 Physiology of truncus arteriosus. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the truncus. Saturated blood returning from the left atrium enters the left ventricle and is also ejected into the truncus. The common aortopulmonary trunk gives rise to the ascending aorta and to the main or branch pulmonary arteries. Oxygen saturation in the aorta and pulmonary arteries is usually the same (definition of a total mixing lesion). As pulmonary vascular resistance decreases in the first few weeks of life, pulmonary blood flow increases dramatically, and mild cyanosis and congestive heart failure result.

(see Fig. 480.6). The demonstration of any vein with Doppler flow away from the heart is pathognomonic of TAPVR because normal venous flow is usually toward the heart. Shunting occurs from right to left at the atrial level. The size of the left atrium and LV can be measured and the presence of any associated cardiac defects determined.

Echocardiography should be adequate to demonstrate TAPVR in most cases; however, if there is question about the drainage of one or more pulmonary veins, cardiac catheterization, MRI, or CTA is performed. Catheterization shows that the oxygen saturation of blood in both atria, both ventricles, and the aorta is similar, indicative of a **total mixing lesion**. An increase in systemic venous saturation occurs at the site of entry of the abnormal pulmonary venous channel, either above or below the diaphragm. In older patients without pulmonary venous obstruction, pulmonary arterial and RV pressure may be only moderately elevated, but in infants with pulmonary venous obstruction, pulmonary hypertension is usual. Selective pulmonary arteriography shows the anatomy of the pulmonary veins and their point of entry into the systemic venous circulation.

Fetal diagnosis of TAPVR is feasible in many, but not all, cases, with the main ultrasonographic signs being ventricular disproportion, increased area behind the left atrium, and the finding of a vertical vein. Color Doppler is key to making this diagnosis. Prenatal diagnosis can be helpful in planning for urgent surgical treatment after birth.

TREATMENT

Surgical correction of TAPVR is performed during early infancy, with emergent repair performed for those patients with venous obstruction. If surgery cannot be performed urgently, extracorporeal membrane oxygenation (ECMO) may be required to maintain oxygenation. Surgically, the pulmonary venous confluence is anastomosed directly to the left atrium, the ASD is closed, and any connection to the systemic venous circuit is interrupted. Early results are generally good, even for critically ill neonates. The postoperative period may be complicated by pulmonary artery hypertensive crises. In some patients, especially those in whom the diagnosis is delayed or the obstruction is severe, recurrent stenosis and development of pulmonary venoocclusive disease may occur. Attempts have been made to treat recurrent stenosis with surgery, balloon angioplasty, stents, and antiproliferative chemotherapy. The long-term prognosis in patients with recurrent obstruction is poor. In those with aggressive venoocclusive disease, **heart-lung transplantation** may be the only option (see Chapter 492.2).

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480.8 Truncus Arteriosus

Daniel Bernstein

In truncus arteriosus, a single arterial trunk (truncus arteriosus) arises from the heart and supplies the systemic, pulmonary, and coronary circulations. A VSD is always present, with the truncus overriding the defect and receiving blood from both the RV and the LV (Fig. 480.8). The number of truncal valve cusps varies from two to as many as six, and the valve may be stenotic, regurgitant, or both. The pulmonary arteries can arise together from the posterior left side of the persistent truncus arteriosus and then divide into left and right pulmonary arteries **(type I)**. In types II and III truncus arteriosus, no main pulmonary artery is present, and the right and left pulmonary arteries arise from separate orifices on the posterior **(type II)** or lateral **(type III)** aspects of the truncus arteriosus. *Type IV truncus* is a term no longer used because, in this case, there is no identifiable connection between the heart and pulmonary arteries, and pulmonary blood flow is derived from **major aortopulmonary collateral arteries (MAPCAs)** arising from the transverse or descending aorta; this is essentially a form of pulmonary atresia (see Chapter 479.2).

Both ventricles are at systemic pressure, and both eject blood into the truncus. When PVR is relatively high immediately after birth, pulmonary blood flow may be normal; as PVR drops in the first few weeks of life, blood flow to the lungs is greatly increased and heart failure ensues. Truncus arteriosus is a **total mixing lesion** with complete admixture of pulmonary and systemic venous return. Because of the large volume of pulmonary blood flow, clinical cyanosis is usually mild. If the lesion is left untreated, PVR eventually increases, pulmonary blood flow decreases, and cyanosis becomes more prominent (**Eisenmenger physiology**; see Chapter 482.2).

CLINICAL MANIFESTATIONS

The clinical signs of truncus arteriosus vary with age and depend on the level of PVR. In the immediate newborn period, signs of heart failure are usually absent; a murmur and minimal cyanosis may be the only initial findings. If unrepaired, during the next 1-2 months of life,

pulmonary blood flow begins to become torrential and the clinical picture is dominated by heart failure, with still mild cyanosis. Runoff of blood from the truncus to the pulmonary circulation may result in a wide pulse pressure and bounding pulses. These findings will be further exaggerated if truncal valve insufficiency is present. The heart is usually enlarged, and the precordium is hyperdynamic. S_2 is loud and single. A systolic ejection murmur, sometimes accompanied by a thrill, is generally audible along the left sternal border. The murmur is frequently preceded by an early systolic ejection click caused by the abnormal truncal valve. In the presence of truncal valve insufficiency, a medium- to high-pitched early diastolic decrescendo murmur is heard at the mid-left sternal border. An apical mid-diastolic rumbling murmur caused by increased flow through the mitral valve is often audible with the bell of the stethoscope, especially as heart failure develops. Truncus arteriosus is a conotruncal malformation and may be associated with **DiGeorge syndrome**, linked to a deletion of a large region of **chromosome 22q11** (see Chapter 473).

DIAGNOSIS

The ECG shows right, left, or combined ventricular hypertrophy. The chest radiograph also shows considerable variation. Cardiac enlargement will develop over the first several weeks of life and is a result of the prominence of both ventricles. The truncus may produce a prominent shadow that follows the normal course of the ascending aorta and aortic knob; the aortic arch is right sided in 50% of patients. Sometimes a high bulge left of the aortic knob is produced by the main or left pulmonary artery. Pulmonary vascularity is increased after the first few weeks of life. Echocardiography is diagnostic and demonstrates the large truncal artery overriding the VSD and the pattern of origin of the branch pulmonary arteries (Fig. 480.9). Associated anomalies such as an interrupted aortic arch may be noted. Pulsed and color Doppler studies are used to evaluate truncal valve regurgitation. If required, cardiac catheterization shows a left-to-right shunt at the ventricular level, with right-to-left shunting into the truncus. Systolic pressure in both ventricles and the truncus is similar. Angiography reveals the large truncus arteriosus and better defines the origin of the pulmonary arteries.

TREATMENT

Most centers perform routine neonatal repair shortly after diagnosis. If surgery is delayed and PVR falls over the first several weeks of life, heart failure symptoms will worsen. Anticongestive medications can be used to better prepare these patients for surgery; however, delay of surgery much beyond this time period may increase the likelihood of developing pulmonary vascular disease. At surgery, the VSD is closed, the pulmonary arteries are separated from the truncus, and continuity is established between the RV and the pulmonary arteries with a homograft conduit. Immediate surgical results are excellent, but these conduits will develop either regurgitation or stenosis over time and must be replaced, often several times, as the child grows. If regurgitation is the primary problem, patients can now be treated with a transcatheter stent-valve (see Chapter 479.1)

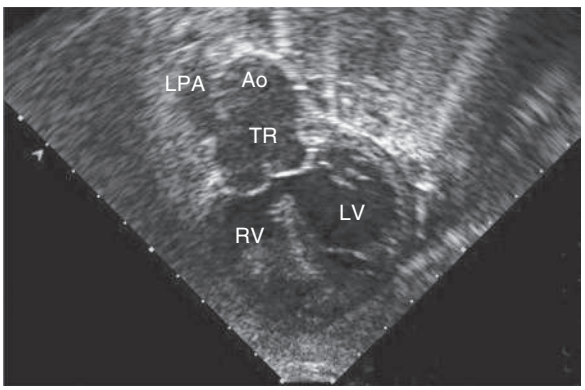

Fig. 480.9 Subcostal 2D echocardiographic demonstration of truncus arteriosus. The large truncal valve can be seen overriding the ventricular septal defect. In this case, only the left pulmonary artery (LPA) arises from the truncus (TR). The pulmonary arteries are discontinuous, and the right pulmonary artery arises from the descending aorta via the ductus arteriosus (not shown). Ao, Aorta; LV, left ventricle; RV, right ventricle.

PROGNOSIS AND COMPLICATIONS

Surgical results have been excellent, and many patients with repaired truncus are now entering mid-adulthood, with several centers reporting 30- and 40-year-old survivors. The need to replace the RV-to-pulmonary artery conduit as the child grows means that these patients will need to undergo multiple operations by the time they reach adulthood. The development of transcatheter stent-valves may reduce this in the future (see Chapter 472). When truncus arteriosus is associated with DiGeorge syndrome, the associated endocrine, immunologic, craniofacial, and airway abnormalities may complicate recovery.

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480.9 Single Ventricle (Double-Inlet Ventricle, Univentricular Heart)

Daniel Bernstein

With a single ventricle, both atria empty through a common atrioventricular valve or through two separate valves into a single ventricular chamber, with total mixing of systemic and pulmonary venous return. This chamber may have left, right, or indeterminate (both right and left) ventricular morphologic characteristics. The aorta and pulmonary artery both arise from this single chamber, although one of the great vessels may originate from a rudimentary outflow chamber. The aorta may be posterior, anterior (malposition), or side-by-side with the pulmonary artery and either to the right or to the left. Pulmonary stenosis or atresia is common.

CLINICAL MANIFESTATIONS

The clinical picture is variable and depends on the associated intracardiac anomalies. If pulmonary outflow is obstructed, the findings are usually similar to those of tetralogy of Fallot: marked cyanosis without heart failure. If pulmonary outflow is unobstructed, the findings are similar to those of transposition with VSD: minimal cyanosis with increasing heart failure.

In patients with **pulmonary stenosis**, cyanosis is present in early infancy. Cardiomegaly is mild or moderate, a left parasternal lift is palpable, and a systolic thrill is common. The systolic ejection murmur is usually loud; an ejection click may be audible, and S_2 is single and loud. In patients with **unobstructed pulmonary flow**, as PVR drops, torrential pulmonary blood flow develops, and these patients present with tachypnea, dyspnea, failure to thrive, and recurrent pulmonary infections. Cyanosis is only mild or moderate. Cardiomegaly is generally marked, and a left parasternal lift is palpable. A systolic ejection murmur is present but is not usually loud or harsh, and S_2 is loud and closely split. A third heart sound (S_3) is common and may be followed by a short mid-diastolic rumbling murmur caused by increased flow through the atrioventricular valves. The eventual development of pulmonary vascular disease reduces pulmonary blood flow so that the cyanosis increases and signs of cardiac failure appear to improve (**Eisenmenger physiology**; see Chapter 482.2).

DIAGNOSIS

ECG findings are nonspecific. P waves are normal, spiked, or bifid. The precordial lead pattern suggests right ventricular hypertrophy, combined ventricular hypertrophy, or sometimes left ventricular dominance. The initial QRS forces are usually to the left and anterior. Radiographic examination confirms the degree of cardiomegaly. If present, a rudimentary outflow chamber may produce a bulge on the upper left border of the cardiac silhouette in the posteroanterior projection. In the absence of pulmonary stenosis, pulmonary vasculature is

increased, whereas in the presence of pulmonary stenosis, pulmonary vasculature is diminished. Echocardiography will confirm the absence or near-absence of the ventricular septum and can usually determine whether the single ventricle has right, left, or mixed morphologic features. The presence of a rudimentary outflow chamber under one of the great vessels can be identified, and pulsed Doppler can be used to determine whether flow through this communication (known as a **bulboventricular foramen**) is obstructed.

If cardiac catheterization is performed, the pressure in the single ventricular chamber is at systemic level; however, a gradient may be demonstrated across the entrance to the rudimentary outflow chamber. Pressure measurements and angiography demonstrate whether pulmonary stenosis is present.

TREATMENT

If pulmonary stenosis is severe, a **Blalock-Taussig aortopulmonary shunt** is performed to provide a reliable source of pulmonary blood flow (see Chapter 479.1). If pulmonary blood flow is unrestricted, pulmonary arterial banding is used to control heart failure and prevent progressive pulmonary vascular disease. The **bidirectional Glenn shunt** is usually performed at 2-4 months of age, followed by a **modified Fontan operation** (cavopulmonary isolation procedure; see Chapter 479.4) at 2-3 years. If subaortic stenosis is present because of a restrictive connection to a rudimentary outflow chamber (*restrictive* bulboventricular foramen), surgical relief can be provided by anastomosing the proximal pulmonary artery to the side of the ascending aorta **(Damus-Stansel-Kaye operation)**.

PROGNOSIS AND COMPLICATIONS

Unoperated, some patients succumb during infancy from heart failure. Others may survive to adolescence and early adult life but finally succumb to the effects of chronic hypoxemia or, in the absence of pulmonary stenosis, to the effects of pulmonary vascular disease. Patients with moderate pulmonary stenosis have the best prognosis because pulmonary blood flow, though restricted, is still adequate. Surgical palliation, eventually leading to Fontan-type circulatory physiology (see Chapter 479.4), has very good short- and intermediate-term results.

480.10 Hypoplastic Left Heart Syndrome

Daniel Bernstein

The term *hypoplastic left heart syndrome* (HLHS) is used to describe a related group of anomalies that include various degrees of underdevelopment of the left side of the heart: stenosis or atresia of the aortic and mitral valves and hypoplasia of the left ventricular cavity and ascending aorta. HLHS categories are based on anatomic characteristics: (1) mitral and aortic atresia (MA-AA), (2) mitral stenosis with aortic atresia (MS-AA), and (3) mitral and aortic stenosis (MS-AS). The LV may be only moderately hypoplastic, very small and nonfunctional, or totally atretic. The LV cavity may be slitlike, miniaturized, or small and thick walled with endocardial fibroelastosis. In patients with MS-AA, there may be anomalous connections between the ventricle and the coronary arteries, which some reports associate with an increased postoperative risk.

The etiology of HLHS may be the result of poor left-sided fetal blood flow (no flow–no grow hypothesis). Alternatively, there may be intrinsic defects of myogenic and endocardial programming affecting differentiation, proliferation, maturation, and apoptosis. Although no single gene is associated with all patients, multiple genes *(GJA1, NKX2-5, SAP130, PCDHA, Notch 1, MY46)* and pathways (transforming growth factor beta [TGF-β], Wnt) have been implicated.

In the immediate neonatal period, the RV maintains both the pulmonary circulation and the systemic circulation via the ductus arteriosus (Fig. 480.10). Pulmonary venous blood passes through an ASD (which may or may not be restrictive) or dilated foramen ovale from the left to the right side of the heart, where it mixes with systemic venous blood (total mixing lesion). Minimal (mitral stenosis subtypes)

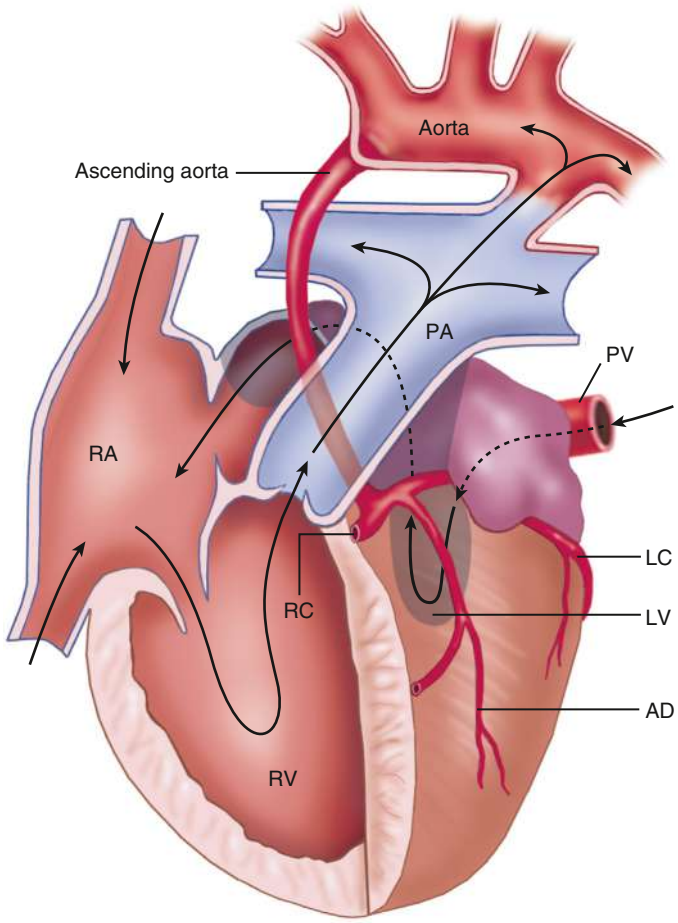

Fig. 458.10 Hypoplastic left heart with aortic hypoplasia, aortic valve atresia, and a hypoplastic mitral valve and left ventricle. AD, Anterior descending; LC, left circumflex; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RC, right coronary artery; RV, right ventricle. *(From Webb GD, Smallhorn, JF, Therrien J, et al. Congenital heart disease in the adult and pediatric patient. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 75-28, p. 1548. Adapted from historical illustrations in Neufeld HN, Adams P Jr, Edwards JE, et al. Diagnosis of aortic atresia by retrograde aortography. Circulation. 1962;25:278; and Edwards JE, Dry TJ, Parker RL, et al. An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield: Charles C. Thomas; 1954.)*

or no (mitral atresia subtype) blood enters the hypoplastic LV. All the RV blood is ejected into the main pulmonary artery, where it then supplies both the descending and the ascending aorta (retrograde flow) via the ductus arteriosus. The major hemodynamic abnormalities are inadequate maintenance of the systemic circulation and, depending on the size of the atrial-level communication, either pulmonary venous hypertension (restrictive foramen ovale) or pulmonary overcirculation (moderate or large ASD).

CLINICAL MANIFESTATIONS

Although cyanosis may not always be obvious in the first 48 hours of life, a grayish-blue skin color is soon apparent and denotes a mix of cyanosis and poor perfusion. The condition is diagnosed in most infants in the first few hours or days of life. Once the ductus arteriosus begins to close, signs of poor systemic perfusion and shock predominate. All the peripheral pulses may be weak or absent. A palpable RV parasternal lift may be present along with a nondescript systolic murmur.

This lesion may be isolated or associated in 5–15% of patients with known genetic syndromes, such as Turner syndrome; trisomy 13, 18, or 21; Jacobsen syndrome (11q deletion); Holt-Oram syndrome; and Rubinstein-Taybi syndrome. In these circumstances, noncardiac

manifestations of the syndrome may be evident and influence the clinical outcomes. Occasionally, HLHS is familial and inherited as an autosomal recessive or dominant trait; there are also families with constellations of different severities of left-sided obstructive lesions, ranging from bicuspid aortic valve, to coarctation of the aorta, to Shone complex, to HLHS.

DIAGNOSIS

On chest radiograph, the heart is variable in size in the first days of life, but cardiomegaly develops rapidly and is associated with increased pulmonary vascularity. The initial ECG may show only the normal neonatal pattern of RV dominance, but later, P waves become prominent and RV hypertrophy is usual with reduced LV forces. The echocardiogram is diagnostic and demonstrates hypoplasia or atresia of the mitral valve and aortic root, a variably small left atrium and LV, and a large right atrium and RV (Fig. 480.11). The size of the atrial communication, by which pulmonary venous blood leaves the left atrium, is assessed by pulsed and color flow Doppler studies. The small ascending aorta and transverse aortic arch are identified; a discrete coarctation of the aorta in the juxtaductal area may be present, although in the presence of a large ductus, it may be difficult to identify. Doppler echocardiography demonstrates whether the mitral and aortic valves are severely stenotic or totally atretic. The presence of left ventricular–to–coronary sinusoidal connections can be identified. The diagnosis of HLHS can usually be made without the need for cardiac catheterization. If catheterization is necessary, the hypoplastic ascending aorta is demonstrated by angiography.

TREATMENT

Surgical therapy for HLHS is associated with improved survival rates, reported as high as 90–95% for the first-stage palliation in experienced centers. The first-stage repair is designed to construct a reliable source of systemic blood flow arising from the single RV using a combination of aortic and pulmonary arterial tissue and to limit pulmonary blood flow to avoid heart failure and prevent the development of pulmonary vascular disease. The surgical procedure typically used is the **Norwood procedure** (Fig. 480.12) or the **Sano procedure**. Primary heart transplantation, previously advocated by a few centers, is much less common because of the substantially improved survival rates with standard surgery and the limited supply of donor organs in this age-group.

Preoperative medical management includes maintaining ductus arteriosus patency with PGE_1 (0.05-0.1 μg/kg/min) to support systemic blood flow, avoiding excess pulmonary blood flow, and maintaining adequate flow from the left to the right atrium. Correction of acidosis and hypoglycemia and prevention of hypothermia are also key components. Excessive pulmonary blood flow, which worsens as the PVR begins to fall, can lead to both respiratory distress and systemic hypoperfusion. This can be prevented through managing ventilator settings to keep the P_{CO_2} in the 45-50 mm Hg range and avoiding supplemental oxygen (which acts as a pulmonary vasodilator) if the system arterial O_2 saturation is in the 70-80 mm Hg range. If the atrial septum is restrictive, a Rashkind balloon atrial septostomy, septal balloon dilation, or rarely, a blade septostomy of the atrial septum may be indicated.

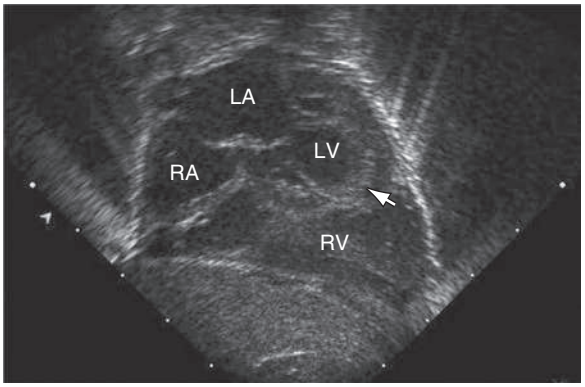

Fig. 480.11 Subcostal 2D echocardiographic diagnosis of hypoplastic left heart syndrome. The small left ventricular chamber can be seen, the apex of which *(arrowhead)* does not form the apex of the heart. The atrial septum can be seen bowing from the left to the right, indicating that the communication between the two atria is pressure restrictive. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

The Norwood or Sano procedure is usually performed in three stages. **Stage I** (see Fig. 480.12), usually performed in the first week of life, includes an atrial septectomy and transection and ligation of the distal main pulmonary artery; the proximal pulmonary artery is then connected to the transversely opened hypoplastic aortic arch to form a "neoaorta," extending through the coarcted segment of the juxtaductal aortic arch. In the Norwood operation, a synthetic aortopulmonary (Blalock-Taussig) shunt connects the aorta to the main pulmonary artery to provide controlled pulmonary blood flow. In the Sano modification, an RV–to–pulmonary artery conduit is used instead of an aortopulmonary shunt to provide pulmonary blood flow, temporarily creating a double-outlet RV. The operative risk for these first-stage procedures has improved dramatically in the past 2 decades, and the best reported results demonstrate a 90–95% survival rate. After the first stage, the patient's oxygen saturation usually ranges from 75% to 85% because of the continued admixture of oxygenated and deoxygenated blood in the right atrium. In the past, there was a high interstage mortality rate in infants discharged from the hospital between stages I and II. This has largely been prevented by performing careful interstage surveillance in home monitoring programs run by pediatric cardiac centers.

Stage II consists of a Glenn shunt anastomosis to connect the superior vena cava to the pulmonary arteries (see Chapter 480.4) at 2-6 months of age. **Stage III**, usually performed at 2-3 years, consists of a modified Fontan procedure (cavopulmonary isolation) to connect the inferior vena cava to the pulmonary arteries via either an intraatrial or external baffle. After stage III, all systemic venous return enters the pulmonary circulation directly. Pulmonary venous flow enters the left atrium and is directed across the atrial septum to the tricuspid valve and subsequently to the right (now the systemic) ventricle. Blood leaves the RV via the neoaorta, which supplies the systemic circulation. The old aortic root now attached to the neoaorta provides coronary blood flow. The risks associated with stages II and III are less than those of stage I; interstage mortality (usually between stages I and II) has been dramatically reduced with the use of home monitoring programs and interstage close follow-up. The short- and long-term benefits of using the Norwood vs the Sano procedure remain to be demonstrated.

An alternative therapeutic approach, initially developed for high-risk standard surgical candidates, is to perform a **hybrid procedure** for the first stage. This involves performing a Rashkind balloon atrial septostomy, cardiac catheter laboratory placement of a stent in the ductus arteriosus, and open chest surgical placement of bilateral pulmonary artery bands. After the hybrid procedure, patients can be weaned off prostaglandin and discharged from the hospital. However, after a hybrid procedure, patients need to undergo a more extensive second-stage procedure involving construction of a neoaorta and removal of the pulmonary artery bands.

Another alternative therapy is **cardiac transplantation**, either in the immediate neonatal period, thereby obviating stage I of the Norwood procedure, or after a successful stage I Norwood procedure is performed as a bridge to transplantation. After transplantation, patients usually have normal cardiac function and no symptoms of heart failure; however, these patients have the chronic risk of organ rejection and lifelong immunosuppressive therapy (see Chapter 492.1). The combination of donor shortage and improved results with standard surgical and hybrid procedures has caused most centers to stop recommending transplantation except when associated lesions make the Norwood operation an exceptionally high-risk procedure (e.g., significant coronary artery anomalies) or for patients who develop poor ventricular function at some time after the standard surgical approach.

PROGNOSIS AND COMPLICATIONS

Untreated patients most often succumb during the first few months of life, usually during the first or second week. Up to 30% of infants with HLHS

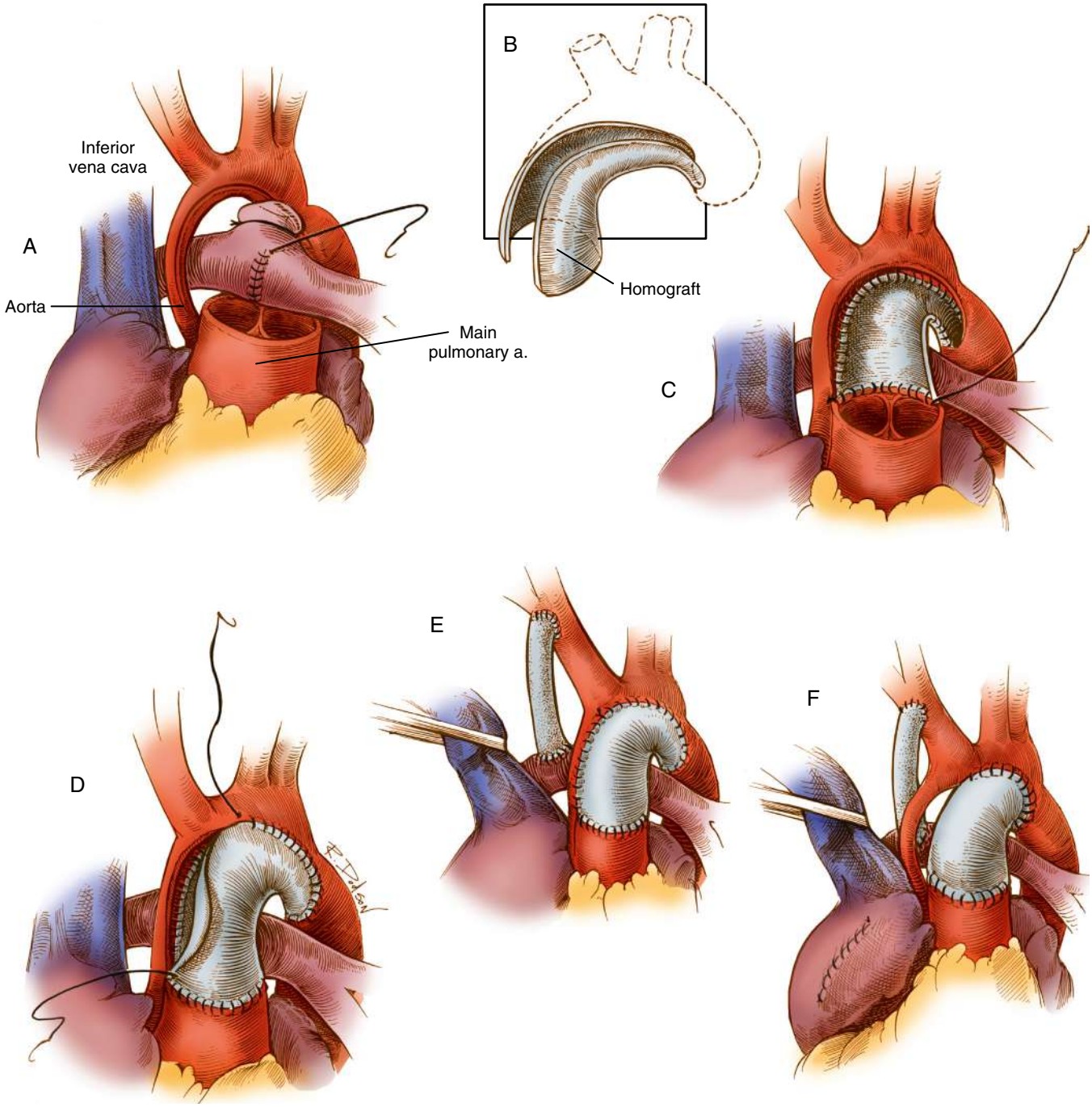

Fig. 480.12 Norwood procedure, one of the two current techniques for first-stage palliation of hypoplastic left heart syndrome. **A,** Incisions used for the procedure incorporate a cuff of arterial wall allograft. The distal divided main pulmonary artery may be closed by direct suture or with a patch. **B,** Dimensions of the cuff of the arterial wall allograft. **C,** The arterial wall allograft is used to supplement the anastomosis between the proximal divided main pulmonary artery and the ascending aorta, aortic arch, and proximal descending aorta. **D** and **E,** The procedure is completed by an atrial septectomy and a 3.5-mm modified right Blalock shunt. **F,** When the ascending aorta is particularly small, an alternative procedure involves placement of a complete tube of arterial allograft. The tiny ascending aorta may be left in situ, as indicated, or implanted into the side of the neoaorta. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al. Single-ventricle tricuspid atresia. In: Cardiac Surgery of the Neonate and Infant. Philadelphia: Saunders; 1994.)*

have evidence of either a major or a minor central nervous system abnormality. Other dysmorphic features may be found in up to 40% of patients. Thus careful preoperative evaluation (genetic, neurologic, ophthalmologic) should be performed in patients being considered for surgical therapy.

Intermediate-term follow-up after completion of all three stages of the Norwood procedure demonstrates generally good exercise capacity and long-term complications equivalent to other patients who have had the Fontan palliation (see Chapter 479.4). Some studies show that patients with HLHS have a higher risk of neurodevelopmental problems than those with other complex congenital heart lesions. Whether the poor neurodevelopmental outcome is the result of genetically associated central nervous system malformations, alteration of prenatal circulation dynamics or prenatal central nervous system injury, complications of bypass surgery, or poor preoperative and/or postoperative perfusion is unknown. Whether a specific HLHS subtype, specifically MS-AA with ventricular-coronary connections, is associated with increased postoperative mortality is still unclear, as studies have shown contradictory results.

PREVENTION

Serial fetal echocardiographic studies demonstrate that in some fetuses, HLHS may be a progressive in utero lesion, beginning with simple valvar aortic stenosis in mid-gestation. The decreased flow through the stenotic aortic valve reduces flow through the LV during development, resulting in gradual ventricular chamber hypoplasia. The potential for preventing this hypoplasia has been demonstrated by performing in utero aortic balloon valvuloplasty in mid-gestation fetuses (Fig. 480.13). Early results are encouraging, although even if the aortic valve is successfully opened, adequate ventricular growth occurs in only ~50% of patients. At present, this procedure is regarded as experimental.

Because of the high mortality of HLHS with an intact or restrictive atrial septum, in utero attempts to improve atrial mixing with either fetal atrial septoplasty or atrial stent placement are undergoing clinical investigation.

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480.11 Abnormal Positions of the Heart and the Heterotaxy Syndromes (Asplenia, Polysplenia)

Daniel Bernstein

Classification and diagnosis of abnormal cardiac position are best performed through a *segmental* approach, with the position of the viscera and atria defined first, then the ventricles, followed by the great vessels (Fig. 480.14). Determination of **visceroatrial situs** can be made by radiographic demonstration of the position of the abdominal organs and the tracheal bifurcation for recognition of the right and left bronchi and by echocardiography. The atrial situs is usually similar to the situs of the viscera and lungs. In **situs solitus** the viscera are in their normal positions (stomach and spleen on the left, liver on the right), the three-lobed right lung is on the right, and the two-lobed left lung on the left; the right atrium is on the right, and the left atrium is on the left. When the abdominal organs and lung lobation are reversed, an arrangement known as **situs inversus** occurs: the left atrium is on the right and the right atrium on the left. If the visceroatrial situs cannot be readily determined, a condition known as **situs indeterminus** or **heterotaxia** exists. The two major heterotaxy syndromes are **asplenia syndrome** (right isomerism or bilateral right-sidedness), which is associated with a centrally located liver, absent spleen, and two morphologic right lungs (Figs. 480.15 and 480.16), and **polysplenia syndrome** (left isomerism or bilateral left-sidedness), which is associated with multiple small spleens, absence of the intrahepatic portion of the inferior vena cava, and two morphologic left lungs (Figs. 480.17 and 480.18). The heterotaxia syndromes are usually associated with severe congenital heart lesions: ASD, VSD, atrioventricular septal defect, hypoplasia of one of the ventricles, pulmonary stenosis or atresia, and anomalous systemic venous or pulmonary venous return (Table 480.2).

Human heterotaxia syndromes may be related to disorders in both motile and primary cilia function and in utero left-right axis development. Genes involved in heterotaxy syndromes, including *NODAL* (known asymmetric gene), and those influenced by *NODAL* such as the TGF-β superfamily *(LEFTY2)* and *Pitx2,* have been implicated in the

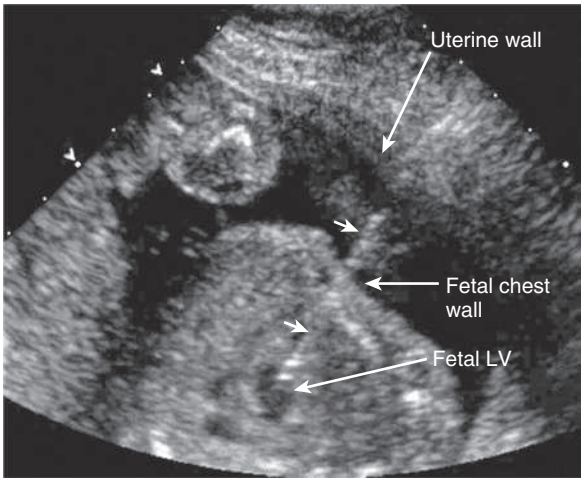

Fig. 480.13 Fetal treatment of critical aortic stenosis to prevent development of hypoplastic left heart syndrome. Fetal ultrasound showing insertion of a needle *(arrowheads)* via the maternal abdominal wall, through the uterus and the fetal chest wall, and into the fetal left ventricle (LV). A balloon catheter is next inserted via the needle into the left ventricular chamber and across the stenotic aortic valve. The balloon is inflated to dilate the valve, and the catheter and needle are removed. *(Courtesy Dr. Stanton Perry, Stanford University, Stanford, CA.)*

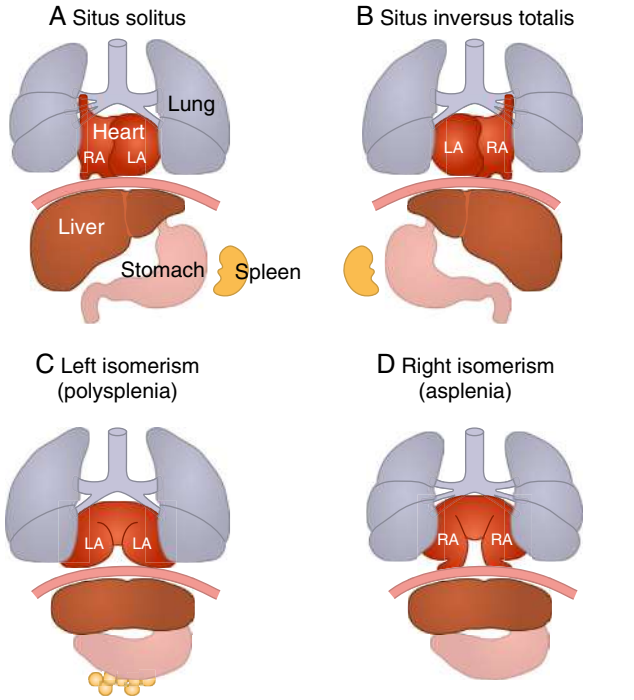

Fig. 480.14 Variations in thoracoabdominal situs in congenital heart disease. **A,** *Situs solitus:* On the right side there is a three-lobed lung, a right atrium (with superior and inferior vena cava entering), and the liver; on the left side there is a two-lobed lung, a left atrium (with pulmonary veins entering), the stomach, and the spleen. **B,** *Situs inversus totalis:* All the structures are mirror-image reversed: On the right side there is a two-lobed lung, a left atrium, the stomach, and the spleen; on the left side there is a three-lobed lung, a right atrium, and the liver. **C,** *Left isomerism (polysplenia):* There are two left sides: On the right side there is a two-lobed lung and a structure that resembles the left atrium; on the left side there is also a two-lobed lung and a structure that resembles the left atrium; there is usually a midline liver and stomach and multiple small spleens. **D,** *Right isomerism (asplenia):* There are two right sides: On the right side there is a three-lobed lung and a structure that resembles the right atrium; on the left side there is also a three-lobed lung and a structure that resembles the right atrium; there is usually a midline liver and stomach and an absent spleen. *(Adapted from Fliegauf M, Benzing T, Omran H. When cilia go bad: cilia defects and ciliopathies. Nat Rev Mol Cell Biol. 2007;8:880–893, Fig. 2.)*

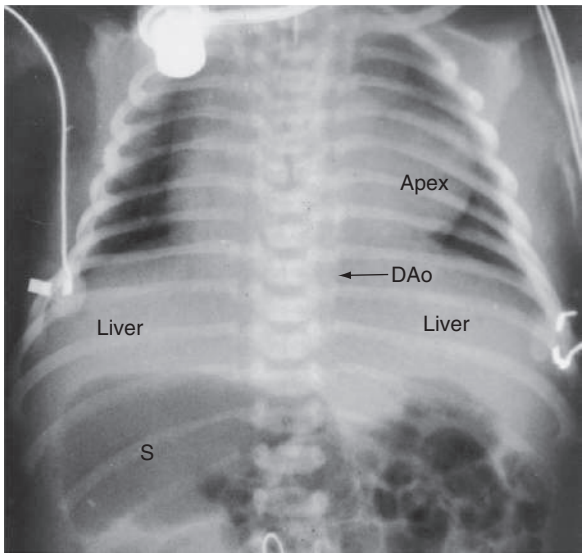

Fig. 480.15 X-ray from asplenic male neonate with right isomerism. The liver is transverse, the stomach (S) is on the right, and the heart is midline, but the base to apex axis points to the left. DAo, Descending aorta. *(Modified from Perloff JK, Marelli AJ. Perloff's Clinical Recognition of Congenital Heart Disease, 6th ed. Philadelphia: Saunders; 2012: Fig. 3-31, p. 32.)*

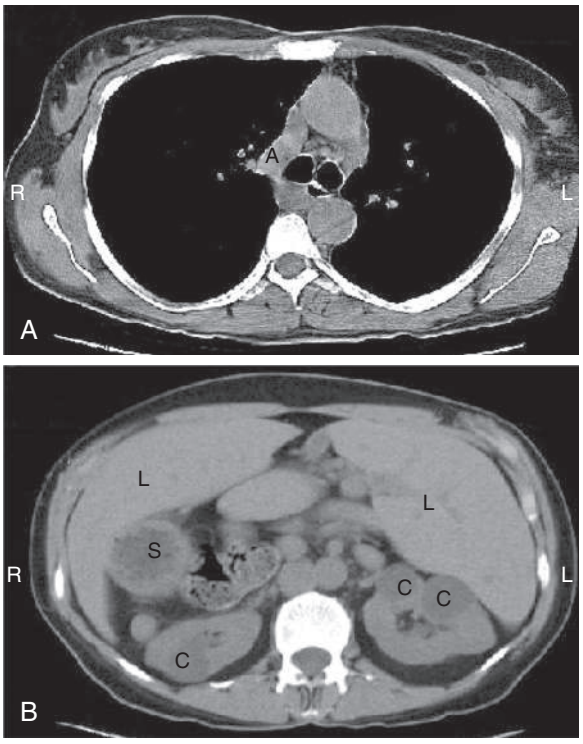

Fig. 480.16 Right isomerism with asplenia. Noncontrast-enhanced CT scan of a female with primary ciliary dyskinesia demonstrates features of right isomerism with asplenia. **A,** Large azygous vein arch is noted, which compensates for the inferior vena cava interruption. **B,** CT scan through the upper abdomen demonstrates midline liver (L), dextrogastria (s), and absent spleen. Bilateral renal cysts (C) are also noted. *(From Chmura K, Chan ED, Noone PG, Zariwala M, Winn RA, Knowles MR, Iseman MD, Gardner EM. A middle-aged woman with recurrent respiratory infections. Respiration. 2005;72(4):427–430.)*

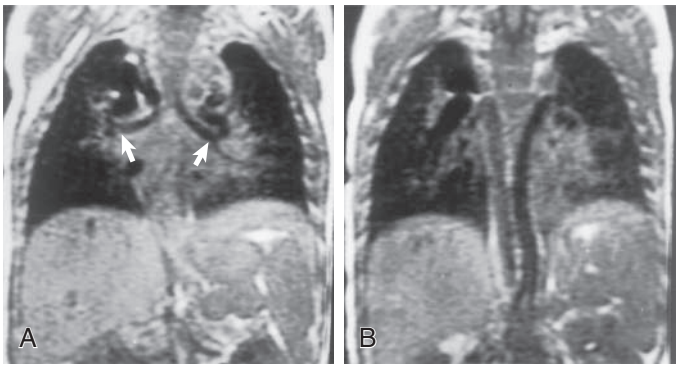

Fig. 480.17 **A,** Coronal T1-weighted MRI of a patient with heterotaxy syndrome (polysplenia) demonstrates a bilateral hyparterial bronchial branching pattern *(arrows)* and left upper quadrant spleens. **B,** More posterior coronal T1-weighted MRI shows left azygos-hemiazygos continuation to the left superior vena cava and right thoracic aorta. *(From Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. Radiographics. 1999;19:837–852, Fig. 4.)*

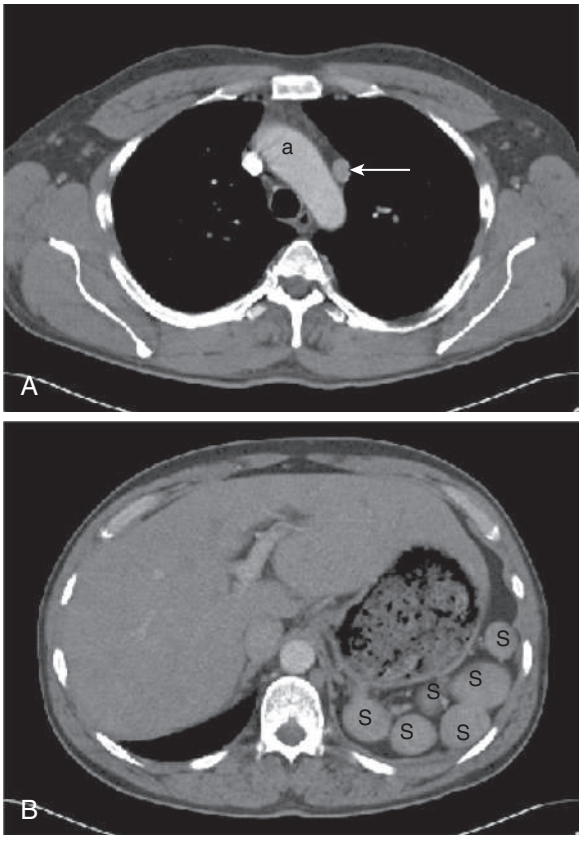

Fig. 480.18 Left isomerism with polysplenia. Contrast-enhanced computed tomography scan of a male with primary ciliary dyskinesia demonstrates features of left isomerism with polysplenia. **A,** Note bilateral superior vena cavae at the level of the aortic arch (a). The right superior vena cava is enhanced after intravenous contrast material administration through a right antecubital vein. Left-sided superior vena cava indicated by *arrow*. **B,** Upper abdomen image demonstrates left upper quadrant splenules (S). *(From Kennedy MP, Omran H, Leigh MW, et al. Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation. 2007;11:2814–2821, Fig. 3.)*

Table 480.2 Comparison of Cardiosplenic Heterotaxy Syndromes

FEATURE	ASPLENIA (RIGHT ISOMERISM)	POLYSPLENIA (LEFT ISOMERISM)
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation or malrotation	Yes	Yes
Risk for midgut volvulus	Yes	Yes
Dextrocardia (%)	30–40	30–40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60–75	15
Total anomalous pulmonary venous return (%)	70–80	Rare
Common atrioventricular valve (%)	80–90	20–40
Single ventricle (%)	40–50	10–15
Absent inferior vena cava with azygos continuation	No	Characteristic
Bilateral superior venae cavae	Yes	Yes
Other common defects	PA, PS, right-sided aortic arch	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

PA, Pulmonary atresia; PS, pulmonary stenosis.

development of heterotaxia syndromes (Fig. 480.19 and Table 480.3). Diagnostic gene panels are available to identify a possible genetic basis.

The next segment is localization of the **ventricles**, which depends on the direction of development of the embryonic cardiac loop. Initial protrusion of the loop to the right **(d-loop**) carries the future RV anteriorly and to the right, whereas the LV remains posterior and on the left (the normal relationship). With situs solitus, a d-loop yields normal atrioventricular connections (right atrium connecting to RV, left atrium to LV). Protrusion of the loop to the left **(l-loop)** carries the future RV to the left and the LV to the right. In this case, in the presence of situs solitus, the right atrium connects with the LV and the left atrium with the RV **(ventricular inversion)**.

The final segment is that of the **great vessels**. With each type of cardiac loop, the ventricular-arterial relationships may be regarded as either normal (RV to pulmonary artery, LV to aorta); transposed (RV to aorta, LV to pulmonary artery); or in the event of a double-outlet ventricle, either normally related or **malposed**. A further classification can be based on the position of the aorta (normally to the right and posterior) relative to the pulmonary artery. In transposition, the aorta is usually anterior and either to the right of the pulmonary artery **(d-transposition)** or to the left **(l-transposition)**.

These segmental relationships can usually be determined by echocardiographic studies demonstrating both atrioventricular and ventriculoarterial relationships. The clinical manifestations of these syndromes of abnormal cardiac position are determined primarily by their associated cardiovascular anomalies.

Dextrocardia occurs when the heart is in the right side of the chest. **Levocardia** (the normal situation) is present when the heart is in the left side of the chest. Dextrocardia without associated situs inversus or levocardia in the presence of situs inversus is most often complicated by other severe cardiac malformations. Surveys of older children and adults indicate that dextrocardia with situs inversus and normally related great arteries ("mirror-image" dextrocardia) is often associated with a functionally normal heart, although congenital heart disease of a less severe nature is common.

Anatomic or functional abnormalities of the lungs, diaphragm, and thoracic cage may result in displacement of the heart to the right **(dextroposition)**. In this case, however, the cardiac apex is pointed

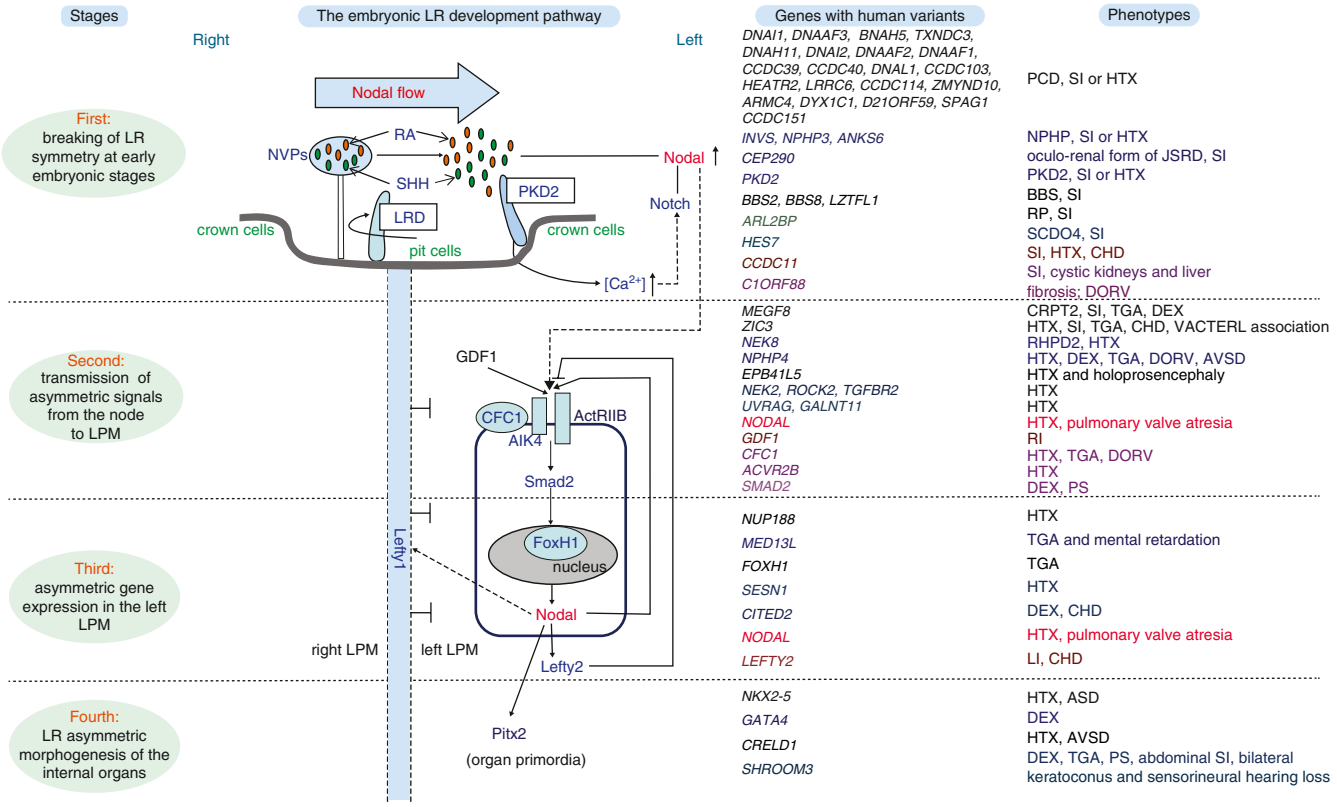

Fig. 480.19 Pathway of left-right (LR) development in the mouse embryo, list of genes associated with human LR asymmetry disorders, and corresponding phenotypes in humans. LRD-containing monocilia generate leftward nodal flow, and polycystin 2–containing cilia sense nodal flow and initiate an asymmetric calcium signal, which induces nodal expression around the node. Nodal signaling is involved in asymmetric morphogenesis by inducing expression of the nodal-responsive genes *(NODAL, LEFTY2,* and *PITX2)* in the left lateral plate mesoderm (LPM) and expression of *LEFTY1* at the midline. Pathogenic variants of genes associated with ciliopathies and nodal signal transduction pathway have been identified in human LR asymmetry disorders. *Full arrows* indicate a direct positive effect on gene expression, *dotted arrows* indicate an indirect effect, and *lines* indicate inhibition. ASD, Atrial septal defect; AVSD, atrioventricular septal defects; BBS, Bardet-Biedl syndrome; CHD, congenital heart disease; CRPT2, Carpenter syndrome 2; DEX, dextrocardia; DORV, double-outlet right ventricle; HTX, heterotaxy; JSRD, Joubert syndrome–related disorders; LI, left isomerism; NPHP, nephronophthisis; NVPs, nodal vesicular parcels; PCD, primary ciliary dyskinesia; PKD2, polycystic kidney disease 2; PS, pulmonary stenosis; RA, retinoic acid; RHPD2, renal-hepatic-pancreatic dysplasia 2; RI, right isomerism; RP, retinitis pigmentosa; SCDO4, spondylocostal dysostosis 4; SHH, sonic hedgehog; SI, situs inversus; TGA, transposition of the great arteries. *(From Deng H, Xia H, Deng S. Genetic basis of human left-right asymmetry disorders. Expert Rev Mol Med. 2014;16:e19, Fig 1.)*

Table 480.3 Ciliopathies with Heterotaxy Defects

CILIOPATHY	FEATURES	GENE(S)	CARDIAC DEFECTS
Primary ciliary dyskinesia	Bronchiectasis, sinusitis, otitis media, infertility, situs defects	*AK7, ARMC4, C21orf59, CCDC103, CCDC114, CCDC151, CCDC39, CCDC40, CCDC65, CCNO, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH11, DNAH5, DNAH6, DNAI2, DNAL1, DNAJB13, DRC1, DYX1C1, GAS8, HEATR2, HYDIN, LRRC6, MCIDAS, NME8, PIH1D3, RPGR, TXNDC3, RSPH1, RSPH3, RSPH4A, RSPH9, SPAG1, TTC25, ZMYND10*	Dextrocardia; heterotaxy spectrum heart defects in ~12%; heterotaxy not thought to occur with genes associated with central pair or radial spoke
Meckel-Gruber syndrome	Renal cysts, CNS anomalies (encephalocele), polydactyly, hepatic fibrosis, congenital heart defects	*MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D1, B9D2, TMEM231, KIF14, TMEM107*	Situs inversus; heterotaxy; HLHS
Joubert and related syndromes	Hypoplasia of the cerebellar vermis (molar tooth sign), dysregulated breathing pattern, retinal dystrophy, renal anomalies	*AH1, C5ORF42, CC2D2A, CSPP1, TMEM216, NPHP1, CEP290, TMEM67, RPGRIP1L, INPP5E, TCTN2, MKS1, CEP104, CEP120, CEP41, KIAA0556, PDE6D, PIBF1, TCTN1, TCTN3, ARL13B, CEP41, KIAA0586, TMEM237, TMEM231, TMEM138, KIAA0753, TMEM107, KIF7, OFD1, C2CD3, IFT172, ARL13B, ZNF423, TTC21B, PDE60, POC18, B9D2, B9D1*	Laterality defects; heart defects, including septal defects, aortic valve anomalies, coarctation; in some cases, associated with features of OFD

Table 480.3 Ciliopathies with Heterotaxy Defects—cont'd

CILIOPATHY	FEATURES	GENE(S)	CARDIAC DEFECTS
Short rib thoracic dysplasias, including Jeune chondrodysplasia, Saldino-Mainzer	Skeletal dysplasia; thoracic deformities; polydactyly; renal cysts; retinitis pigmentosa	*IFT80, DYNC2H1, TTC21B, WDR19, NEK1, WDR35, WDR60, IFT140, IFT172, WDR34, CEP120, KIAA0586, DYNC2LI1, IFT52, TCTEX1D2*	Rare; septal defects, laterality defects
Carpenter syndrome	Acrocephaly; polysyndactyly, hypogenitalism, obesity, congenital heart defects	*RAB23, MEGF8, RAB23*	PDA, PS, VSD, situs inversus, heterotaxy

HLHS, Hypoplastic left heart syndrome; OFD, oral-facial-digital; PDA, patent ductus arteriosus; PS, pulmonary stenosis; and VSD, ventricular septal defect.
Modified from Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation*. 2018;138(21):e653–e711, Table 6.

normally to the left, as opposed to dextrocardia, where the cardiac apex is pointed to the right or anteriorly. This anatomic position is less often associated with congenital heart lesions, although hypoplasia of a lung may be accompanied by anomalous pulmonary venous return from that lung (**scimitar syndrome**; see Chapter 475.4).

The ECG is difficult to interpret in the presence of lesions with discordant atrial, ventricular, and great vessel anatomy. Diagnosis usually requires detailed echocardiographic and sometimes MRI, CT, or cardiac catheterization studies. The **prognosis** and **treatment** of patients with one of the cardiac positional anomalies are determined by the underlying defects and are covered in their respective chapters. Asplenia increases the risk of serious infections, such as bacterial (usually pneumococcal) sepsis, and thus requires daily antibiotic prophylaxis. Patients with polysplenia frequently have poor splenic function and also require prophylaxis against bacterial sepsis. Patients with heterotaxia are also at increased risk of intestinal malrotation and volvulus and of ciliary dyskinesia and associated pulmonary complications (see Chapters 101.3 and 455).

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Chapter 481

Other Congenital Heart and Vascular Malformations

481.1 Anomalies of the Aortic Arch

Daniel Bernstein

RIGHT AORTIC ARCH

In this abnormality, the aorta curves to the right and, if it descends on the right side of the vertebral column, is usually associated with other cardiac malformations. It is found in 20% of cases of tetralogy of Fallot and is also common in truncus arteriosus. A right aortic arch without other cardiac anomalies is not associated with symptoms. It can often be visualized on the chest radiograph. The trachea is deviated slightly to the left of the midline rather than to the right, as in the presence of a normal left arch. On a barium esophagogram, MRI, or CT scan, the esophagus is indented on its right border at the level of the aortic arch.

VASCULAR RINGS

Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression (Table 481.1). The origin of these lesions can best be appreciated by reviewing the embryology of the aortic arch (see Fig. 469.1). The most common anomalies include (1) double aortic arch (Fig. 481.1A), (2) right aortic arch with a left ligamentum arteriosum, (3) anomalous innominate artery arising farther to the left on the arch than usual, (4) anomalous left carotid artery arising farther to the right than usual and passing anterior to the trachea, (5) anomalous right subclavian artery, and (6) anomalous left pulmonary artery **(vascular sling)**. In the latter anomaly, the abnormal vessel arises from an elongated main pulmonary artery or from the right pulmonary artery. It courses between and compresses the trachea and the esophagus. Associated congenital heart disease may be present in 5–50% of patients, depending on the vascular anomaly.

Clinical Manifestations

If the vascular ring produces compression of the trachea and/or esophagus, symptoms are frequently present during infancy. Chronic wheezing is exacerbated by crying, feeding, and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Choking on solid food and vomiting may also be symptoms. Affected infants may have a brassy cough, pneumonia, or rarely, sudden death from aspiration.

Diagnosis

Standard radiographic examination is not usually helpful. In the past, performing a barium esophagogram was the standard method of diagnosis (Fig. 481.2), which has been replaced by echocardiography in combination with either MRI or CT (Fig. 481.3). Cardiac catheterization is reserved for cases with associated anomalies or in rare cases where these other modalities are not diagnostic. Bronchoscopy is helpful in more severe cases to determine the extent of airway narrowing and whether additional surgery is required on the airway.

Treatment

Surgery is advised for symptomatic patients who have evidence of tracheal compression. The anterior vessel is usually divided in patients with a double aortic arch (see Fig. 481.1B). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. Anomalous innominate or carotid arteries cannot be divided; attaching the adventitia of these vessels to the sternum usually relieves the tracheal compression. An anomalous left pulmonary artery is corrected by division at its origin and reanastomosis to the main pulmonary artery after it has been brought in front of the trachea. Severe tracheomalacia, if present, may require reconstruction of the trachea as well.

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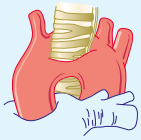
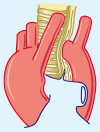
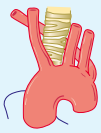
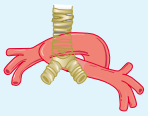
Table 481.1 Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOPY	MRI ECHO	TREATMENT
DOUBLE ARCH 	Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
RIGHT ARCH AND LIGAMENTUM/DUCTUS 	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile	Diagnostic	Ligate ligamentum or ductus
ANOMALOUS INNOMINATE 	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative apnea, then suspend
ABERRANT RIGHT SUBCLAVIAN 	Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
PULMONARY SLING 	Expiratory stridor Respiratory distress	AP—low l. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, Anteroposterior; L and l., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.
From Kliegman RM, Greenbaum LA, Lye PS. *Practical Strategies in Pediatric Diagnosis and Therapy,* 2nd ed. Philadelphia: Elsevier; 2004:88.

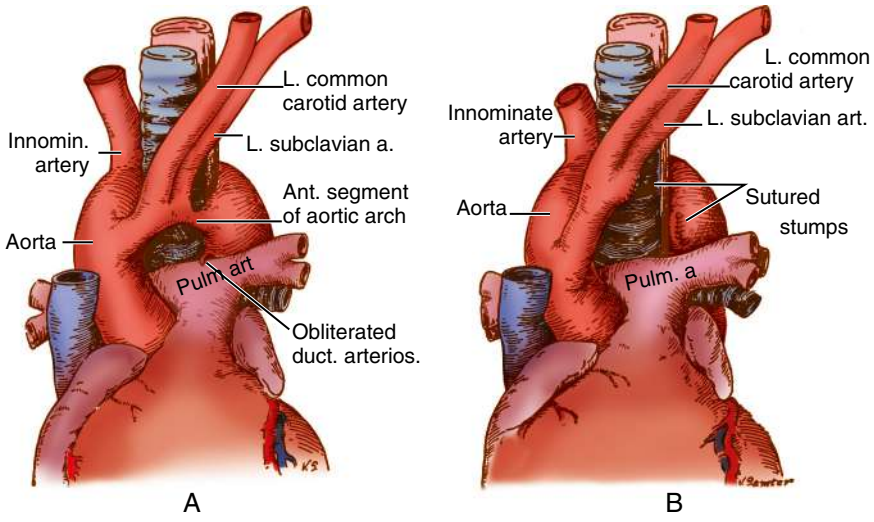


Fig. 481.1 Double aortic arch. **A,** Small anterior segment of the double aortic arch (most common type). **B,** Operative procedure for release of the vascular ring. L., Left; a. and art., artery; ant., anterior; innom., innominate; duct. arterios., ductus arteriosus; pulm., pulmonary.

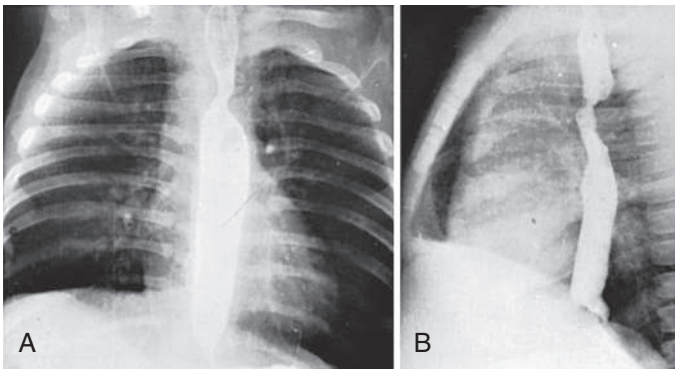


Fig. 481.2 Double aortic arch in an infant age 5 mo. **A,** Anteroposterior view. The barium-filled esophagus is constricted on both sides. **B,** Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at surgery.

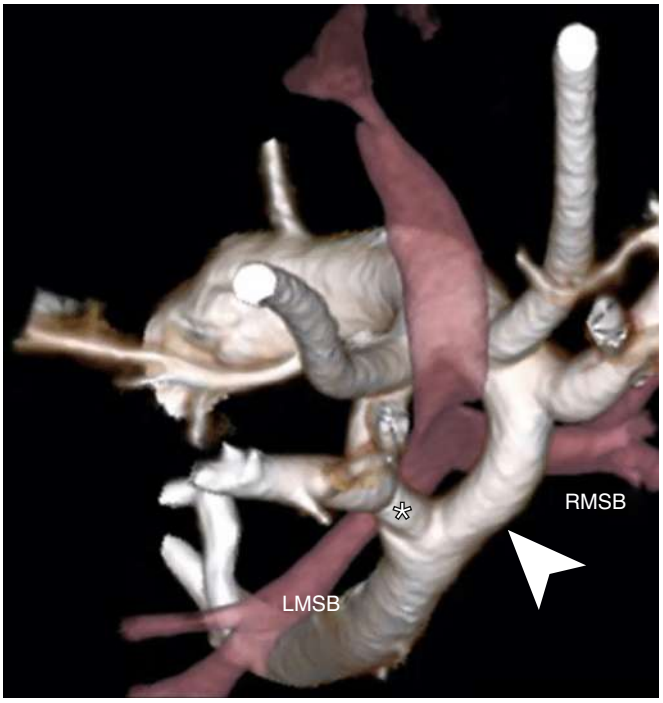


Fig. 481.3 Double aortic arch in a 12-year-old. Superior (bird's eye view) three-dimensional volume-rendered CT image shows the larger dominant arch *(arrowhead)* on the right side, coursing over the right mainstem bronchus *(RMSB).* There is mild indentation of the trachea. The smaller left arch *(asterisk)* courses over the left mainstem bronchus *(LMSB). (From Madueme PC: Computed tomography and magnetic resonance imaging of vascular rings and other things: a pictorial review. Pediatr Radiol 2022;52:1839–1848.(Fig. 2, p. 1840.)*

481.2 Anomalous Origin of the Coronary Arteries

Daniel Bernstein

Table 481.2 provides a classification system for coronary artery anomalies. Although many of these are isolated, congenital anomalies of the coronary arteries may also be seen in patients with congenital heart disease (tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries, single ventricle, tricuspid atresia, truncus arteriosus, quadricuspid or bicuspid aortic valves, double-outlet ventricle). In addition, acquired lesions of the coronary arteries associated with existing congenital heart disease may develop because of alterations in blood flow or postoperative stenoses, especially in patients whose surgery involves the aortic root.

Table 481.2 Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease

ANOMALOUS AORTIC ORIGIN
• Eccentric ostium within an aortic sinus
• Ectopic ostium above an aortic sinus
• Conus artery from the right aortic sinus
• Circumflex coronary artery from the right aortic sinus or from the right coronary artery
• Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
• Atresia of the left main coronary artery
• Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
• Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
• Origin of a single coronary artery from the right or left aortic sinus
• Anomalous origin from a noncardiac systemic artery
ANOMALOUS AORTIC ORIGIN WITH ANOMALOUS PROXIMAL COURSE
• Acute proximal angulation
• Ectopic right coronary artery passing between aorta and pulmonary trunk
◦ Ectopic left main coronary artery
◦ Between aorta and pulmonary trunk
◦ Anterior to the pulmonary trunk
◦ Posterior to the aorta
• Within the ventricular septum (intramyocardial)
• Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk
ANOMALOUS ORIGIN OF A CORONARY ARTERY FROM THE PULMONARY TRUNK
• Left main coronary artery
• Left anterior descending coronary artery
• Right coronary artery
• Both right and left coronary arteries
• Circumflex coronary artery
• Accessory coronary artery

From Perloff JK, Marelli J. *Perloff's Clinical Recognition of Congenital Heart Disease,* 6th ed. Philadelphia: Saunders; 2012: Table 32-3, p. 532.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY

In anomalous origin of the left coronary artery from the pulmonary artery **(ALCAPA)**, the blood supply to the left ventricular (LV) myocardium is severely compromised. Soon after birth, as pulmonary artery pressure falls, perfusion pressure to the left coronary artery (LCA) becomes inadequate; myocardial ischemia, infarction, and fibrosis result. In some cases, interarterial collateral anastomoses develop between the right coronary artery (RCA) and LCA. Blood flow in the LCA is then reversed, and it empties into the pulmonary artery, a condition known as *myocardial steal syndrome.* The LV becomes dilated, and its performance is decreased. Mitral insufficiency is a frequent complication secondary to a dilated valve ring or infarction of a papillary muscle. Localized aneurysms may also develop in the LV free wall. Rare patients have adequate myocardial blood flow during childhood and, later in life, a continuous murmur and a small left-to-right shunt via the dilated coronary system (aorta to RCA to LCA to pulmonary artery).

Clinical Manifestations

Evidence of heart failure becomes apparent within the first few months of life and may be exacerbated by respiratory infection. Recurrent attacks of discomfort, restlessness, irritability, sweating, dyspnea, and pallor occur and represent an infantile version of **angina pectoris**. Diagnosis is often made only after a chest x-ray is obtained looking for other sources of irritability and rapid breathing. Cardiac enlargement ranges from moderate to massive. A gallop rhythm is common.

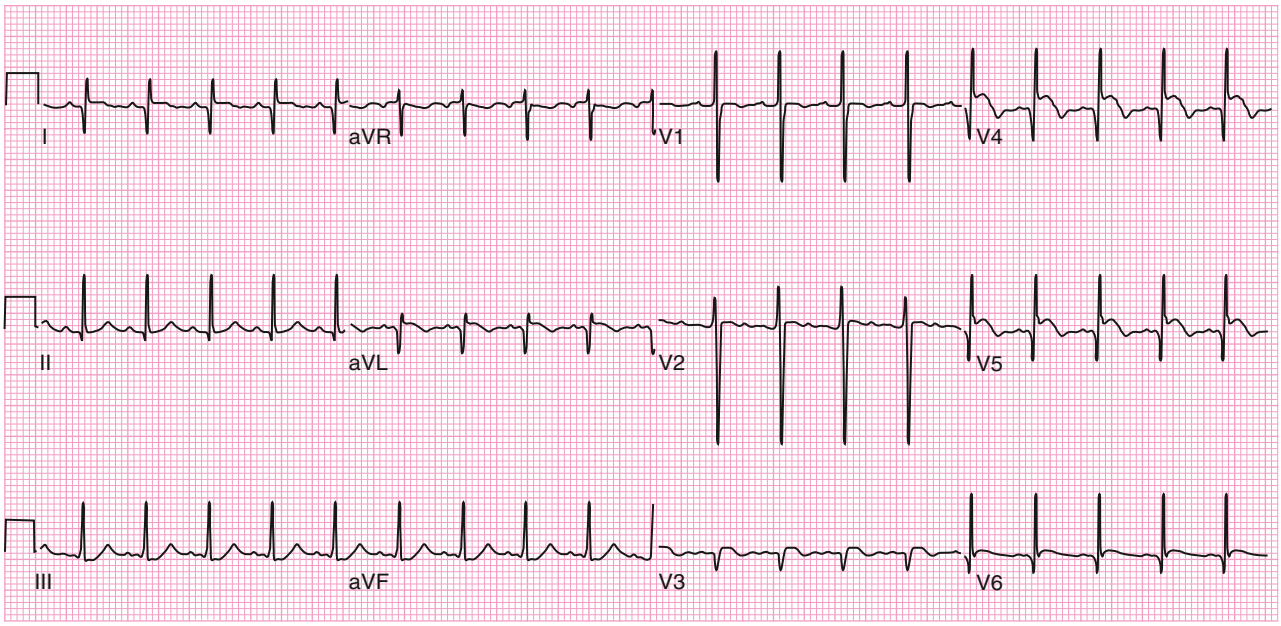


Fig. 481.4 Electrocardiogram of a 2-mo-old with anomalous origin of the left coronary artery from the pulmonary artery. Myocardial infarction is evidenced by abnormal Q waves in leads I and aVL and in the anterolateral precordial leads (V_3, V_4, V_5, V_6). There is also ST elevation in leads V_4 and V_5, a sign of ongoing ischemia. Another sign of ALCAPA is the diminution or loss of R waves in the midprecordial leads (V_2, V_3).

Murmurs may be of the nonspecific ejection type or may be holosystolic because of mitral insufficiency. Older patients with abundant intercoronary anastomoses may have continuous murmurs and less LV dysfunction. However, during older childhood and adolescence, they may experience angina during exercise. Rare patients with an anomalous RCA may also have such clinical findings, especially if the RCA supplies the inferoposterior portion of the LV (right dominant system).

Diagnosis

Radiographic examination confirms cardiomegaly. The electrocardiogram (ECG) can resemble the pattern described in anterolateral wall myocardial infarction in adults, although this pattern can vary over the first weeks of life. A QR pattern followed by flattened or inverted T waves is typically seen in leads I and aVL (Fig. 481.4). The anterolateral precordial leads (V_3-V_6) may show deep Q waves or elevated ST segments and inverted T waves (the more typical adult findings of a lateral myocardial infarction) or may be relatively normal. Decreased or absent R waves may be seen over the mid-precordial leads (V_3, V_4). Given the subtlety of these ECG findings and that an infarct pattern is not usually expected in infants, a high index of suspicion should be maintained for patients with the symptoms described earlier. Two-dimensional (2D) echocardiography with color Doppler usually confirms the diagnosis; however, in rare cases, echocardiography may not be definitive in diagnosing this condition. On 2D imaging alone, the LCA may appear as though it is arising from the aorta. Color Doppler ultrasound has improved the accuracy of diagnosis of this lesion, demonstrating the presence of retrograde flow in the LCA. If needed, CT or MRI can confirm the origin of the coronary arteries. Cardiac catheterization is also diagnostic; aortography shows immediate opacification of the RCA only. In patients who have developed collaterals, this vessel is large and tortuous. After filling of the intercoronary anastomoses, the LCA is opacified, and contrast can be seen to enter the pulmonary artery. Pulmonary arteriography should opacify the origin of the anomalous LCA. Selective left ventriculography usually demonstrates a dilated LV that empties poorly and mitral regurgitation.

Treatment and Prognosis

Untreated, death often occurs from heart failure within the first 6 months of life. Those who survive without surgery generally have abundant intercoronary collateral anastomoses. Medical management includes standard therapy for heart failure (diuretics, angiotensin-converting enzyme inhibitors, and β blockers).

Surgical treatment consists of detaching the anomalous coronary artery from the pulmonary artery and anastomosing it to the aorta to establish normal myocardial perfusion. In patients who have already sustained a significant myocardial infarction, cardiac transplantation may be the only option (see Chapter 492.1).

ANOMALOUS ORIGIN OF THE RIGHT CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous origin of the RCA from the pulmonary artery is not usually manifested in infancy or early childhood. The LCA is enlarged, whereas the RCA is thin walled and mildly enlarged. In early infancy, perfusion of the RCA is from the pulmonary artery, whereas later, perfusion is from collaterals of the left coronary vessels. Angina and sudden death can occur in adolescence or adulthood. When recognized, this anomaly should be repaired by reanastomosis of the RCA to the aorta.

ANOMALOUS AORTIC ORIGIN OF A CORONARY ARTERY

In anomalous aortic origin of a coronary artery (AAOCA), one or both coronary arteries arise from their nonusual sinus (e.g., LCA from the right sinus of Valsalva) or high on the aorta, above the sinotubular junction. There are multiple anatomic variations, with different physiologic consequences, and therefore with different risks of coronary ischemia, arrhythmia, and potentially sudden death. Fortunately, most variants of AAOCA are benign, and the challenge for clinicians is to recognize which variants place their patient at a greater risk of a life-threatening event.

The aberrant artery may be a left, right, or major branch coronary artery. The site of origin may be the wrong sinus of Valsalva (anomalous origin of a coronary artery from the opposite sinus, **ACAOS**) or a proximal coronary artery. The ostium may be hypoplastic, slitlike, or of normal caliber. The aberrant vessel may pass anteriorly, posteriorly, or between the aorta and right ventricular outflow tract (RVOT); it may take an intramural course, tunneling in the conal or interventricular septal tissue. Obstruction resulting from hypoplasia of the ostia, tunneling between the aorta and RVOT or interventricular septum, and acute angulation produce myocardial ischemia and infarction. Although unobstructed vessels usually produce no

Table 481.3 Classification of Coronary Anomalies Based on Ischemia

ISCHEMIA	CLASSIFICATION
Absence of ischemia	Most anomalies (split RCA, ectopic RCA from right cusp; ectopic RCA from left cusp)
Episodic ischemia	Anomalous origin of a coronary artery from the opposite sinus (ACAOS); coronary artery fistulas; myocardial bridge
Typical ischemia	Anomalous left coronary artery from the pulmonary artery (ALCAPA); coronary ostial atresia or severe stenosis

RCA, Right coronary artery.
From Mehran R, Dangas GD. Coronary angiography and intravascular imaging. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease,* 11th ed. Philadelphia: Elsevier; 2019: Fig. 20.8, p. 385.

symptoms (Table 481.3), patients with coronary obstruction may initially present with an acute coronary event, either acute myocardial infarction, ventricular arrhythmias, angina pectoris, or syncope; sudden death may occur, especially in young athletes.

Diagnostic modalities include ECG, 2D echocardiography, CT or MRI, radionuclide perfusion scan, and cardiac catheterization with selective coronary angiography. Exercise stress testing can play an important role in assessing risk (e.g., in patients who present only with chest pain), but is usually contraindicated in those who present with a sudden cardiac arrest, documented ischemia, or ventricular arrhythmia.

Treatment is indicated for obstructed vessels, for patients with symptoms, and for those who present with a sudden cardiac event and consists of reanastomosis of the aberrant vessel to the correct aortic sinus. The management of asymptomatic patients with ectopic coronary origin without obstruction remains controversial, as the ability to predict risk is still incompletely understood. Management decisions should be based on the specific anatomy, results of laboratory investigations, and shared decision-making with patients and their families after careful explanation of risks and benefits. Surgery is not without complications and should be performed at centers experienced in AAOCA surgery.

The risk appears to be highest with anomalous LCA from the right sinus of Valsalva with interarterial course (see Table 481.3); however, there are patients with anomalous RCA who are also at risk.

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481.3 Pulmonary Arteriovenous Fistula

Daniel Bernstein

Fistulous vascular communications in the lungs may be large and localized or multiple, scattered, and small. The most common form of this unusual condition is **Osler-Weber-Rendu syndrome** (hereditary hemorrhagic telangiectasia type I), which is also associated with angiomas of the nasal and buccal mucous membranes, gastrointestinal (GI) tract, or liver. Pathogenic variants in the endoglin gene, a cell surface component of the transforming growth factor (TGF)-β receptor complex, cause this syndrome. The usual communication is between the pulmonary artery and pulmonary vein; direct communication between the pulmonary artery and left atrium is extremely rare. Desaturated blood in the pulmonary artery is shunted through the fistula into the pulmonary vein, thus bypassing the lungs, and then enters the left side of the heart, *resulting in systemic arterial desaturation and sometimes clinically detectable cyanosis.* The shunt across the fistula is at low pressure and resistance, so pulmonary artery pressure is normal; cardiomegaly and heart failure are not present.

The clinical manifestations depend on the magnitude of the shunt. Large fistulas are associated with dyspnea, cyanosis, clubbing, a continuous murmur, and polycythemia. Hemoptysis is rare, but when it occurs, it may be massive. Features of Osler-Weber-Rendu syndrome are seen in approximately 50% of patients (or other family members) and include recurrent epistaxis and GI tract bleeding. Transitory dizziness, diplopia, aphasia, motor weakness, or convulsions may result from cerebral thrombosis, abscess, or paradoxical emboli. Soft systolic or continuous murmurs may be audible over the site of the fistula. The ECG is normal. Chest radiographs may show opacities produced by large fistulas; multiple small fistulas may be visualized by fluoroscopy (as abnormal pulsations), MRI, or CT. Selective pulmonary arteriography demonstrates the site, extent, and distribution of the fistulas.

Treatment consisting of excision of solitary or localized lesions by lobectomy or wedge resection results in complete disappearance of symptoms. In most patients, fistulas are so widespread that surgery is not possible. Any direct communication between the pulmonary artery and the left atrium can be obliterated.

Patients who have undergone a **Glenn cavopulmonary anastomosis** for cyanotic congenital heart disease (see Chapter 479.4) are also at risk for the development of pulmonary **arteriovenous malformations** (AVMs). In these patients the AVMs are usually multiple, and the risk increases over time after the Glenn procedure. Pulmonary AVMs rarely occur after full palliation by completion of the **Fontan operation**. This finding suggests that the pulmonary circulation requires an as-yet-undetermined hepatic factor to suppress the development of AVMs. The hallmark of the development of pulmonary AVMs is a gradual decrease in the patient's oxygen saturation, which is usually lower than normal to begin with. The diagnosis can often be made with contrast echocardiography; cardiac catheterization is the definitive test. Completion of the Fontan circuit, so that inferior vena cava blood flow (containing hepatic venous drainage) is routed through the lungs, usually results in improvement or resolution of the malformations.

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481.4 Ectopia Cordis

Daniel Bernstein

In the most common thoracic form of ectopia cordis, the sternum is split and the heart protrudes outside the chest. In other forms, the heart protrudes through the diaphragm into the abdominal cavity or may be situated in the neck. Associated intracardiac anomalies are seen in 40% (tetralogy of Fallot, conotruncal lesions). **Pentalogy of Cantrell** consists of ectopia cordis, midline supraumbilical abdominal defect, deficiency of the anterior diaphragm, defect of the lower sternum, and an intracardiac defect (ventricular septal defect, tetralogy of Fallot, or diverticulum of the left ventricle). Death may occur early in life, usually from infection, cardiac failure, or hypoxemia. Surgical therapy for neonates without overwhelmingly severe cardiac anomalies consists of covering the heart with skin without compromising venous return or ventricular ejection. Repair or palliation of associated defects is also necessary.

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481.5 Diverticulum of the Left Ventricle

Daniel Bernstein

Left ventricular diverticulum is a rare anomaly in which the diverticulum protrudes into the epigastrium. The lesion may be isolated or associated with complex cardiovascular anomalies. A pulsating mass is usually visible and palpable in the epigastrium. Systolic or systolic-diastolic murmurs produced by blood flow into and out of the diverticulum may be audible over the lower part of the sternum and the mass. The ECG shows a pattern of complete or incomplete left bundle branch block. The chest radiograph may or may not show the mass. Associated abnormalities include defects of the sternum, abdominal wall, diaphragm, and pericardium (see earlier). Surgical treatment of the diverticulum and associated cardiac defects can be performed in selected cases. Occasionally, a diverticulum may be small and not associated with clinical signs or symptoms. These small diverticula are diagnosed at echocardiographic examination for other indications.

Chapter 482
Pulmonary Hypertension

482.1 Primary Pulmonary Hypertension

Daniel Bernstein and Rachel K. Hopper

Pulmonary hypertension (PH) refers to an elevated pressure in the pulmonary arteries and is associated with significant morbidity and mortality in children. The etiologies of PH are varied, but all lead to similar symptoms and can ultimately result in right-sided heart failure (Tables 482.1 and 482.2). PH is often characterized by progressive vascular disease of the pulmonary arteries (pulmonary arterial hypertension [PAH], previously called *primary PH*). PH occurs at any age, although in pediatric patients the mean age at diagnosis is 7-10 years. In patients with idiopathic or familial PAH, females outnumber males 1.7:1; in other patients, both genders are represented equally. Pathogenic variants in the *BMPR2* gene, a member of the transforming growth factor (TGF)-β receptor family, on chromosome 2q33 have been identified in 70% of patients with **familial pulmonary arterial hypertension** and in 10–20% with idiopathic sporadic PAH (see Table 482.2). Other potential disease-causing genes include *ALK1* and *ENG* (both associated with hereditary hemorrhagic telangiectasia) and *SMAD9, CAV1, KCNK3,* and *SOX17* (associated with congenital heart disease and PAH). *TBX4* is associated with developmental lung disease and PAH. Viral infection, such as with the vasculotropic human herpesvirus 8, has been suggested as a trigger factor in some patients.

PAH is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles (Fig. 482.1). Secondary remodeling may be found in the larger pulmonary arteries as well. **Pulmonary venoocclusive disease**, mixed precapillary and postcapillary vascular disease, may account for some cases of PAH. Before a diagnosis of PAH can be made, other causes of elevated pulmonary artery pressure must be eliminated; these include chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, left-sided heart disease, recurrent pulmonary emboli, developmental lung disease, liver disease, autoimmune disease, and moyamoya disease (see Table 482.1). PAH accounts for nearly half of all pediatric PH (45%), with PAH associated with congenital heart disease being the most common in pediatric patients, followed by idiopathic or familial disease. PH associated with chronic lung disease is growing to encompass a larger portion of new cases, nearly half of all pediatric PH (49%). Bronchopulmonary dysplasia related to prematurity and other developmental lung diseases are increasingly recognized as contributing to PH in children (see Table 482.2).

PH places an afterload burden on the right ventricle, which results in right ventricular hypertrophy (RVH). Dilation of the pulmonary artery is present, and pulmonary valve insufficiency may occur. In the later stages of the disease, the right ventricle dilates, tricuspid insufficiency develops as the tricuspid valve leaflets are pulled apart, and cardiac output is decreased. Arrhythmias, syncope, and sudden death are known complications.

CLINICAL MANIFESTATIONS

The predominant symptoms include exercise intolerance (dyspnea) and fatigability; occasionally, precordial chest pain, dizziness, or headaches are noted. Syncope may be noted in approximately 30% of pediatric patients. Patients often undergo an incorrect evaluation and are treated for asthma or seizures before a proper diagnosis is made. Peripheral cyanosis may be present, especially during exercise or in patients with a patent foramen ovale or other intracardiac communication through which blood can shunt from right to left. In the late stages of disease, patients may have cold extremities and a gray appearance associated with low cardiac output. Arterial oxygen-hemoglobin saturation is usually normal unless there is an associated intracardiac shunt. If right-sided heart failure has supervened, jugular venous pressure is elevated, and hepatomegaly and edema are present. Jugular venous *a* waves are present, and in those with functional tricuspid insufficiency, a conspicuous jugular *cv* wave and systolic hepatic pulsations are manifested. The heart is moderately enlarged, and a right ventricular heave can be noted. The first heart sound is often followed by an ejection click emanating from the dilated pulmonary artery. The second heart sound (S_2) is narrowly split, with a loud pulmonic component that is sometimes booming in quality; it is frequently palpable at the upper left sternal border. A presystolic (S_4) gallop rhythm may be audible at the lower left sternal border. The systolic murmur is soft and short and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency. In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

DIAGNOSIS

Chest radiographs reveal a prominent pulmonary artery and right ventricle (Fig. 482.2). The pulmonary vascularity in the hilar areas may be prominent, in contrast to the peripheral lung fields in which pulmonary markings are decreased. The electrocardiogram (ECG) shows RVH, often with spiked P waves. Echocardiography is used to screen for any congenital cardiac malformations and assess right ventricular size and function. Doppler evaluation of the tricuspid valve, if insufficiency is present, will allow estimation of the right ventricular (and thus pulmonary arterial) systolic pressure.

At cardiac catheterization, the presence of left-sided obstructive lesions (pulmonary venous stenosis, mitral stenosis, restrictive cardiomyopathy) that result in pulmonary venous hypertension can be evaluated (see Chapters 476.9, 480.7, and 488.3). Elevated pulmonary artery pressures with a normal pulmonary capillary wedge pressure and high vascular resistance is diagnostic of PAH. If the wedge pressure is elevated and left ventricular end-diastolic pressure (LVEDP) is normal, obstruction at the level of the pulmonary veins, left atrium, or mitral valve should be suspected. If LVEDP is also elevated, the diagnosis of restrictive cardiomyopathy should be entertained. The risks associated with cardiac catheterization are increased in severely ill patients with PAH and should occur at centers with expertise in pediatric PH.

PROGNOSIS AND TREATMENT

Many forms of PAH are progressive, and no cure is currently available. Figure 482.3 provides a general treatment approach to PH. Current medical therapies are pulmonary vasodilatory agents, which relieve symptoms, improve quality of life, and delay clinical worsening; however, they do not stop the progression of the disease. Some success has been reported with oral **calcium channel blockers (CCBs)** such as nifedipine in children who demonstrate pulmonary vasoreactivity when these agents are administered during catheterization. Continuous intravenous infusion of the arachidonic acid metabolite **prostacyclin** (epoprostenol) provides relief as long as the infusion is continued and has been shown to improve survival in children with PAH. **Treprostinil**, a prostacyclin analog with a longer half-life, has also been shown to be effective. Nebulized and oral forms of prostacyclin, as well as other oral pulmonary vasodilators, such as endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, have been used with success in adults and in a small number of clinical studies in children (Table 482.3). In patients with PH secondary to left-sided heart disease or lung disease, pulmonary vasodilators should only be considered after optimization of the underlying condition and in consultation with a PH expert.

Anticoagulation may be of value in patients with previous pulmonary thromboemboli; some of these patients may respond to balloon angioplasty of narrowed pulmonary artery segments. Riociguat, a soluble guanylate cyclase stimulator, with vasorelaxation, antiproliferation, and antifibrotic properties, has proved effective in adults with chronic thromboembolic or idiopathic PH. Diuretics are often used to manage right heart failure. Despite many advances, definitive therapy is still lung transplantation (see Chapter 492.2). Palliative interventions may

Table 482.1 Classification of Pulmonary Hypertension (PH)*

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug- and toxin-induced PAH
   - 1.4 PAH associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistosomiasis
   - 1.5 PAH long-term responders to calcium channel blockers
   - 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   - 1.7 Persistent PH of the newborn syndrome
2. Pulmonary hypertension due to left heart disease
   - 2.1 PH due to heart failure with preserved LVEF
   - 2.2 PH due to heart failure with reduced LVEF
   - 2.3 Valvular heart disease
   - 2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Obstructive lung disease
   - 3.2 Restrictive lung disease
   - 3.3 Other lung disease with mixed restrictive/obstructive pattern
   - 3.4 Hypoxia without lung disease
   - 3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions
   - 4.1 Chronic thromboembolic pulmonary hypertension
   - 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   - 5.1 Hematologic disorders
   - 5.2 Systemic and metabolic disorders
   - 5.3 Others
   - 5.4 Complex congenital heart disease.

*Modified as compared with the Nice 2013 classification.
HIV, Human immunodeficiency virus; PVOD, pulmonary venoocclusive disease; PCH, pulmonary capillary hemangiomatosis, LVEF, left ventricular ejection fraction.
From Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913.

Table 482.2 Developmental and Genetic Lung Diseases Associated with Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Down syndrome
Noonan syndrome
Alveolar capillary dysplasia (ACD) with "misalignment of veins" *(FOXF1)*
Cobalamin C deficiency
Lung hypoplasia, acinar dysplasia
Surfactant protein abnormalities
Surfactant protein B deficiency
Surfactant protein C deficiency
ATP-binding cassette A3 variants
Thyroid transcription factor 1 (TTF1)/*Nkx2.1* homeobox pathogenic variants
T-box transcription factor 4 *(TBX4)*
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia
Other pathogenic variants (*BMPR2, ACVRL1, EIF2AK4, CAV1, ENG, KCNK3, SMAD9, SOX17*)

Adapted with data from Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J.* 2019;53(1):1801916; and Ivy DD, Abman SH, Barst RJ et al. Pediatric pulmonary hypertension. *J Amer Coll Cardiol.* 2013;62(25):Suppl D, D118–D126, 2013.

include atrial septostomy or a surgical Potts shunt to create a right-to-left shunt as a pop-off to allow decompression of the right ventricle (see Fig. 482.3). In patients with severe PH and low cardiac output, the terminal event is often sudden and related to a lethal arrhythmia. Patients with PH diagnosed in infancy, especially those in premature infants with chronic lung disease, have a high risk of early mortality, but PH generally improves over time if lung growth and protection from infection and injury are achieved. Infants with PH caused by pulmonary vein stenosis often have rapid progression and high mortality.

482.2 Pulmonary Vascular Disease (Eisenmenger Syndrome)

Daniel Bernstein and Rachel K. Hopper

The term *Eisenmenger syndrome* refers to patients with an intracardiac defect or aortopulmonary connection through which blood is shunted

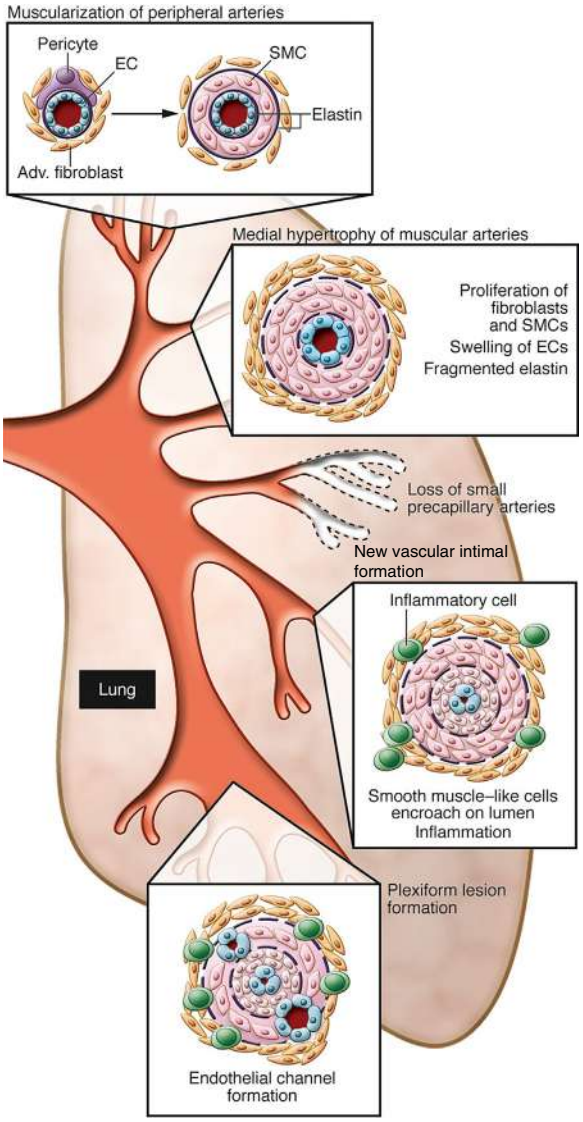

Fig. 482.1 Vascular abnormalities associated with pulmonary arterial hypertension: abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arterioles, and new vascular intimal formation that is occlusive in vessels <500-100 μM and in plexiform lesions therein. Adv. adventitial; EC, endothelial cell; SMC, smooth muscle cell. *(From Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest. 2012;122:4306–4313, Fig 1.)*

partially or totally from right to left as a result of the development of pulmonary vascular disease. This physiologic abnormality can occur with unrepaired ventricular or atrioventricular septal defects, patent ductus arteriosus, aortopulmonary window, or any other communication between the aorta and pulmonary artery and in many forms of complex congenital heart disease with unrestricted pulmonary blood flow. Pulmonary vascular disease with an isolated atrial septal defect can occur, but this is less common and usually does not occur until late in adulthood.

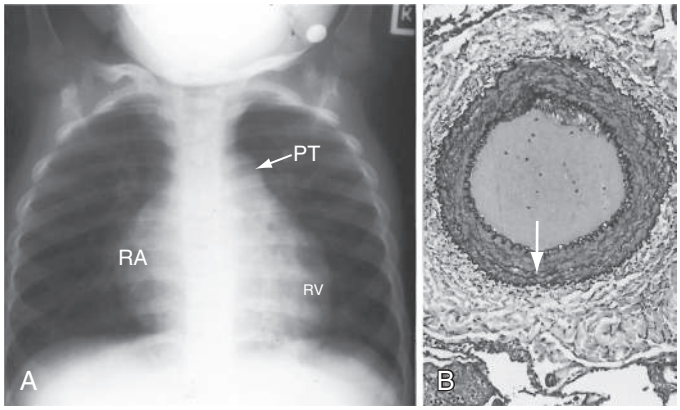

Fig. 482.2 A, Radiograph from a 3-yr-old child with pulmonary arterial hypertension. Pulmonary vascularity is reduced. The pulmonary trunk (PT), right atrium (RA), and right ventricle (RV) are considerably enlarged. B, Histology of an intrapulmonary artery at necropsy shows medial hypertrophy *(arrow). (From Perloff JK, Marelli AJ. Perloff's Clinical Recognition of Congenital Heart Disease, 6th ed. Philadelphia: Saunders; 2012: Fig. 14-17, p. 207.)*

In Eisenmenger syndrome, pulmonary vascular resistance (PVR) after birth either remains high or, after having decreased during early infancy, rises thereafter because of chronic increased shear stress on pulmonary arterioles. Factors playing a role in the rapidity of development of pulmonary vascular disease include increased pulmonary artery pressure, increased pulmonary blood flow, and the presence of hypoxia or hypercapnia. Early in the course of disease, PH is the result of markedly increased pulmonary blood flow (*hyperkinetic* PH). This form of PH decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, PH is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary vessels). This form of PH is usually only minimally responsive to pulmonary vasodilators or oxygen or may be totally unresponsive.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathologic changes of Eisenmenger syndrome occur in the small pulmonary arterioles and muscular arteries (<300 μm) and are graded on the basis of histologic characteristics **(Heath-Edwards classification)**:

- **Grade I** change involves medial hypertrophy alone.
- **Grade II** consists of medial hypertrophy and intimal hyperplasia.
- **Grade III** involves near-obliteration of the vessel lumen.
- **Grade IV** includes arterial dilation.
- **Grades V and VI** include plexiform lesions, angiomatoid formation, and fibrinoid necrosis.

Grades IV-VI indicate irreversible pulmonary vascular obstructive disease. Eisenmenger physiology is usually defined by an absolute elevation in pulmonary arterial resistance to >12 Wood units (resistance units indexed to body surface area) or by a ratio of pulmonary-to-systemic vascular resistance of ≥1.0.

Pulmonary vascular disease occurs more rapidly in patients with trisomy 21 who have left-to-right shunts. It also complicates the natural history of patients with elevated pulmonary venous pressure secondary to mitral stenosis or left ventricular dysfunction,

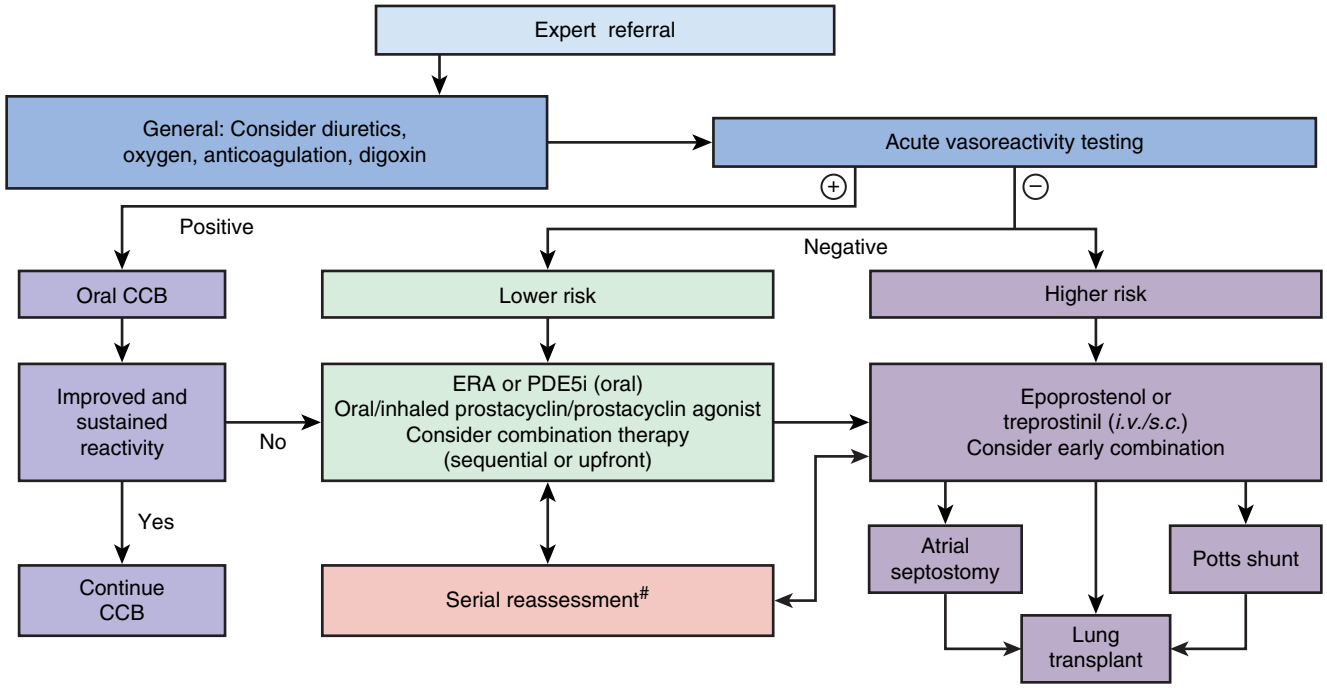

Fig. 482.3 6th World Symposium on Pulmonary Hypertension Consensus pediatric idiopathic/familial PAH treatment algorithm. Use of all agents is considered off-label in children aside from sildenafil in Europe and bosentan in age >3 yr in the United States. CCB, Calcium channel blocker; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; IV, intravenous; PDE-5i, phosphodiesterase-5 inhibitor; SC, subcutaneous; PO, by mouth; #, deterioration or not meeting treatment goals. *(From Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53[1]:1801916.)*

Table 482.3 Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI_2], a potent vasodilator; also inhibits platelet aggregation)	1-2 ng/kg/min initially Increase based on clinical course and tolerance to 5-80 ng/kg/min Some patients may require even higher doses Must be given by continuous infusion that is not interrupted	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain, foot and bone pain
Iloprost (synthetic analog of PGI_2)	2.5-5.0 μg 6-9 times daily (limited data in children) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI_2)	1-2 ng/kg/min initially Target dose ranges from 20-80 ng/kg/min Given either IV or SC via continuous infusion Longer half-life than epoprostenol *Inhaled:* 6-54 mcg (1-9 patient activated breaths) every 6 hr *Oral:* initially 0.125 mg 3 times daily Target dose ranges from 1 to 10 mg 3 times daily	Flushing, headache, diarrhea, hypotension, jaw pain Pain at infusion site when given SC Inhaled form can exacerbate reactive airway symptoms Increased gastrointestinal side effects with oral formulation
Selexipag (prostacyclin IP receptor agonist)	50-1600 mcg PO twice daily; limited data in children	Headache, pain in jaw, joints or limbs, myalgias, nausea, vomiting, diarrhea, flushing
Ambrisentan (selective endothelin EtA receptor antagonist)	Target dose ranges from 1.25 to 10 mg daily; use ½ dose for first mo	Flushing, headache, hypotension, fluid retention/edema, nasopharyngitis/congestion, vomiting; teratogenicity risk
Bosentan (nonselective endothelin receptor EtA and EtB antagonist)	Starting dose: 0.3-1 mg/kg/dose twice daily PO for first mo For patients <10 kg: max. 2 mg/kg/dose twice daily; 10-20 kg: max. 2 mg/kg/dose twice daily (32 mg tablets); 20-40 kg: 62.5 mg/dose twice daily; >40 kg: 125 mg/dose twice daily	Flushing, headache, hypotension, nasopharyngitis/congestion, fluid retention, edema, vomiting, anemia, elevated transaminases (monthly LFTs required); teratogenicity risk. Caution in concomitant use of CYP3A4 inducers and inhibitors
Macitentan (nonselective endothelin receptor EtA and EtB antagonist)	5-10 mg daily PO; limited data in children	Flushing, headache, fluid retention/edema, anemia, nasopharyngitis/congestion; teratogenicity risk.
Sildenafil (phosphodiesterase type 5 inhibitor)	0.5-1 mg/kg/dose given 3-4 times daily PO For 10-20 kg, use 10 mg 3 times daily; >20 kg, 20 mg 3 times daily Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, dyspepsia, diarrhea, hypotension, priapism, visual disturbance (blue coloration), tinnitus
Tadalafil (phosphodiesterase type 5 inhibitor)	1 mg/kg/dose given daily PO Maximum adult dose 40 mg daily Initial dosing should be ½ final target dose to evaluate for hypotension	Similar to sildenafil
Riociguat (soluble guanylate cyclase stimulator)	Limited pediatric data Starting adult dose 1 mg tid, can increase to maximum 2.5 mg tid	Hypotension, headache, dizziness, dyspepsia Use with PDE5 inhibitors contraindicated
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used, now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated LFTs

*Modified as compared with the Nice 2013 classification.
Note: These medications should only be administered under the direction of a specialist in pulmonary hypertension.
cGMP, Cyclic guanosine monophosphate; IV, Intravenously; LFT, liver function test; SC, subcutaneously.

especially in those with restrictive cardiomyopathy (see Chapter 488.3). Pulmonary vascular disease can also occur in any patient with transmission of systemic pressure to the pulmonary circulation via a shunt at the interventricular or great vessel level and in patients chronically exposed to low partial pressure of oxygen (because of high altitude). Patients with cyanotic congenital heart lesions associated with unrestricted pulmonary blood flow are at particularly high risk.

CLINICAL MANIFESTATIONS

Symptoms do not usually develop until the second or third decade of life, although a more fulminant course may occur. Intracardiac or extracardiac communications that would normally shunt from left to right are converted to right-to-left shunting as PVR exceeds systemic vascular resistance. Cyanosis becomes apparent, and dyspnea, fatigue, and a tendency toward dysrhythmias begin to occur. In the late stages of the disease, heart failure, chest pain, headaches,

syncope, and hemoptysis may be seen. Physical examination reveals a right ventricular heave and a narrowly split S_2 with a loud pulmonic component. Palpable pulmonary artery pulsation may be present at the left upper sternal border. A holosystolic murmur of tricuspid regurgitation may be audible along the left sternal border. An early decrescendo diastolic murmur of pulmonary insufficiency may also be heard along the left sternal border. The degree of cyanosis depends on the stage of the disease. Clubbing of the distal digits may be seen in late disease as a result of chronic hypoxia.

DIAGNOSIS

On chest radiograph, the heart varies in size from normal to greatly enlarged; the latter usually occurs late in the course of the disease. The main pulmonary artery is generally prominent, similar to other causes of PAH (see Fig. 482.2A). The pulmonary vessels are enlarged in the hilar areas and taper rapidly in caliber in the peripheral branches. The right ventricle and atrium are prominent. The ECG shows marked RVH. The P wave may be tall and spiked. Cyanotic patients have various degrees of polycythemia that depend on the severity and duration of hypoxemia.

The echocardiogram shows a thick-walled right ventricle and demonstrates the underlying congenital heart lesion. 2D echocardiography assists in eliminating from consideration lesions such as obstructed pulmonary veins, supramitral membrane, mitral stenosis, and restrictive cardiomyopathy. Doppler studies demonstrate the direction of the intracardiac shunt and the presence of a typical hypertension waveform in the main pulmonary artery. Tricuspid and pulmonary regurgitation can be used in the Doppler examination to estimate pulmonary artery systolic and diastolic pressures.

Cardiac catheterization usually shows a bidirectional shunt at the site of the defect. Systolic pressure is generally equal in the systemic and pulmonary circulations. Pulmonary capillary wedge pressure is normal unless a left-sided heart obstructive lesion or left ventricular failure is the cause of the PAH. Arterial oxygen-hemoglobin saturation is decreased depending on the magnitude of the right-to-left shunt. The response to vasodilator therapy (oxygen, prostacyclin, nitric oxide) may identify patients with less severe disease. Selective pulmonary artery injections may be necessary if pulmonary venous obstruction is suspected because of high wedge pressure and low LVEDP.

TREATMENT

The best management for patients who are at risk for the development of late pulmonary vascular disease is prevention by early surgical elimination of large intracardiac or great vessel communications during infancy. Some patients may be missed because they have not shown early clinical manifestations. Rarely, PVR never decreases at birth in these infants, and therefore they never acquire enough left-to-right shunting to become clinically apparent. Such delayed recognition is a particular risk in patients with congenital heart disease who live at high altitude. It is also a risk in infants with trisomy 21, who have a propensity for earlier development of pulmonary vascular disease. Because of the high incidence of congenital heart disease associated with trisomy 21, routine echocardiography is recommended at the time of initial diagnosis, even in the absence of other clinical findings.

Medical treatment of Eisenmenger syndrome is primarily symptomatic. Many patients benefit substantially from either oral **(CCBs, endothelin antagonist**, **phosphodiesterase inhibitors)** or chronic continuous intravenous **(prostacyclin)** therapy. Combined heart-lung or bilateral lung transplantation is the only surgical option for many of these patients (see Chapter 492.2). Heart-lung transplantation may be the option if there is associated complex congenital heart disease.

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Chapter 483

General Principles of Treatment of Congenital Heart Disease

Daniel Bernstein

Most patients who have minor congenital heart lesions do not require treatment. The parents and child should be made aware that a normal life is expected and that no restriction of the child's activities is necessary. Overprotective parents may use the presence of a minor congenital heart lesion or even a functional heart murmur as a means to exert excessive control over their child's activities. Although fears may not be expressed overtly, the child may become anxious regarding early death or debilitation, especially when an adult member of the family acquires unrelated symptomatic heart disease. The family may have an unexpressed fear of sudden death, and the rarity of this manifestation should be emphasized in discussions directed at improving their understanding of the child's congenital heart defect. General health maintenance, including a well-balanced "heart-healthy" diet, aerobic exercise, and avoidance of smoking, should be encouraged.

Even patients with moderate to severe congenital heart disease (CHD) need not be restricted from all physical activity, although many will tend to limit their own activities. Physical education should be modified appropriately to the child's capacity to participate; the extent of such modification can be guided by formal exercise testing in an appropriately equipped pediatric exercise laboratory. Although competitive sports for some patients may need to be discouraged, decisions are made on an individual basis. The influence of coach and peer pressure should be considered when recommending competitive vs noncompetitive athletics. Many cardiologists will also prohibit certain high-impact activities ("collision sports") such as tackle football or contact martial arts in patients who have had prior open heart surgery.

Routine immunizations should be given, with the inclusion of influenza vaccine during the appropriate season. Vaccination against the SARS-CoV-2 virus has been recommended for children with heart disease who are eligible based on age. Prophylaxis against respiratory syncytial virus (RSV) is recommended during RSV season in young infants with unrepaired CHD and significant hemodynamic abnormalities or in those with cardiomyopathy and heart failure. Careful consideration of the timing of administration of live-virus vaccination is required in patients who are potential candidates for heart or heart-lung transplantation, and these patients cannot receive live-virus vaccines after they have received their transplant.

Bacterial infections should be treated vigorously. **Prophylaxis against bacterial endocarditis** should be carried out during dental procedures for appropriate patients (see Chapter 486).

Cyanotic patients need to be monitored for noncardiac manifestations of oxygen deficiency (Table 483.1); however, it is rare today for a patient to remain significantly cyanotic beyond the first few years of life, although mild degrees of cyanosis may be seen in patients with a single ventricle (e.g., hypoplastic left heart) who have a fenestration in their Fontan conduits allowing right-to-left shunting. These patients should be carefully observed for excessive **polycythemia**. Cyanotic patients should avoid situations where dehydration may occur, which leads to increased viscosity and increases the risk of stroke. Diuretics may need to be decreased or temporarily discontinued during episodes of acute gastroenteritis or during excessively hot weather. High altitudes and sudden changes in the thermal environment should also be avoided. Treatment of iron deficiency is important in cyanotic patients, who

Table 483.1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy if symptomatic
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Anticoagulation, phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Plastic bronchitis	Fontan procedure	Bronchoscopy, vascular coiling, lymphatic ablation
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic osteoarthropathy	None
Pregnancy complications: miscarriage, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Pregnancy prevention counseling, high-risk obstetric management
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	RSV monoclonal antibodies* (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	s/p Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium-chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Neurodevelopmental disabilities	Chronic hypoxia, cardiac surgery, genetic	Early school-based evaluation and intervention
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

*Palivizumab, nirsevimab.
CNS, Central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; s/p, status post (after).

may have a low mean corpuscular hemoglobin concentration despite polycythemia. The risk of stroke for these patients can be reduced if the red blood cells are not microcytic. Phlebotomy with partial exchange transfusion is carried out only in symptomatic patients with severe polycythemia (usually those with hematocrit >65%).

Patients with moderate to severe forms of CHD or a history of rhythm disturbance should be carefully monitored during anesthesia for even routine surgical or dental procedures. Consultation with an anesthesiologist experienced in the care of children with CHD is recommended even if the surgical procedure is not cardiac related.

Females with unrepaired severe CHD should be counseled on the risks associated with childbearing and on the use of contraceptives and other methods to prevent pregnancy (see Chapter 483.1). Females with mild to moderate CHD and many who have had corrective surgery can have normal pregnancies, although those with residual hemodynamic derangements or with systemic right ventricles (RVs) should be followed by a high-risk perinatologist and a cardiologist with expertise in caring for adults with CHD. Pregnancy may be highly dangerous to both mother and fetus for patients with palliated (rather than repaired) complex CHD, chronic cyanosis, or pulmonary arterial hypertension; for patients with a Fontan circulation, the miscarriage rate has been reported as ranging from 27% to 50% and the rate of prematurity at 69%. Risks to the mother include heart failure, thromboembolism, and arrhythmia. Several risk stratification schemes have been developed for pregnant women with CHD, including the Cardiac Disease in Pregnancy **(CARPREG)** score, the Zwangerschap bij Aangeboren HARtAfwijkingen **(ZAHARA)** score, and the World Health Organization (WHO) classification. Based on the WHO system, patients for whom pregnancy is associated with increased risk of mortality or morbidity include those with a systemic RV (e.g., corrected transposition with good function), Fontan circulation, repaired coarctation of the aorta bicuspid aortic valve with enlarged aortic root of 45-50 mm, **Marfan syndrome** with enlarged aortic root of 40-45 mm, atrioventricular septal defects, moderate mitral stenosis, severe aortic stenosis, and mechanical valve replacement. Patients for whom pregnancy is considered contraindicated include those with pulmonary arterial hypertension, Ehlers-Danlos syndrome, severe recoarctation of the aorta, Fontan circulation with any complications, severe aortic or mitral stenosis, severe aortic dilation, and systemic ventricular dysfunction with ejection fraction <30%.

POSTOPERATIVE MANAGEMENT

After successful open heart surgery, the severity of the congenital heart defect, the age and condition (nutritional status) of the patient before surgery, the events in the operating room (OR), and the quality of the postoperative care influence the patient's course. **Intraoperative** factors that influence survival and that should be noted when a patient returns from the OR include the duration of **cardiopulmonary bypass** (CPB), duration of **aortic cross-clamping** (time the heart is not being perfused), and duration of **profound hypothermia** (used in some newborns; time the entire body is not being perfused). Surgical techniques to provide ongoing perfusion to the upper body and brain even during surgery on the aortic arch (e.g., in hypoplastic left heart syndrome [HLHS]) have eliminated the use of profound hypothermia in many centers.

Immediate postoperative care should be provided in an intensive care unit (ICU) staffed by a team of physicians, nurses, and technicians experienced with the unique problems encountered after open heart surgery in childhood. In most major centers, this occurs in a dedicated pediatric cardiovascular ICU. Preparation for postoperative monitoring begins in the OR, where the anesthesiologist or surgeon places an arterial catheter to allow direct arterial pressure measurements and arterial sampling for blood gas determination. A central venous catheter is also placed for measuring central venous pressure and for infusions of cardioactive medications. In more complex cases, right or left atrial or pulmonary artery catheters may be inserted directly into these cardiac structures and used for pressure monitoring purposes. Temporary pacing wires are placed on the atrium or ventricle, or both, in case temporary postoperative heart block occurs. Transcutaneous oximetry provides for continuous monitoring of arterial oxygen saturation. Near-infrared spectroscopy is used to monitor cerebral and other end-organ perfusion in the perioperative period.

Functional failure of one organ system may cause profound physiologic and biochemical changes in another. Respiratory insufficiency, for example, leads to hypoxia, hypercapnia, and acidosis, which in turn compromise cardiac, vascular, and renal function. The latter problems cannot be managed successfully until adequate ventilation is reestablished. Thus it is essential that the primary source of each postoperative problem be identified and treated.

Respiratory failure is a serious postoperative complication encountered after open heart surgery. CPB performed in the presence of pulmonary congestion results in decreased lung compliance, copious tracheal and bronchial secretions, atelectasis, and increased breathing effort. Because fatigue and subsequently hypoventilation and acidosis may rapidly ensue, mechanical positive pressure endotracheal ventilation is usually continued after open heart surgery for a minimum of several hours in relatively stable patients and for up to 2-3 days or longer in severely ill patients, especially infants. Protocols for early extubation have been successfully used in older children with uncomplicated intraoperative courses. Patients with certain congenital heart lesions, particularly those with **DiGeorge syndrome**, may also have airway abnormalities (micrognathia, tracheomalacia, bronchomalacia) that can make both ventilation and extubation more difficult.

The electrocardiogram (ECG) should be monitored continuously during the postoperative period. A change in heart rate, even without arrhythmia, may be the first indication of a serious complication such as hemorrhage, hypothermia, hypoventilation, or heart failure. **Cardiac rhythm disorders** must be diagnosed quickly because a prolonged untreated arrhythmia may add a severe hemodynamic burden to the heart in the critical early postoperative period (see Chapter 484). Injury to the heart's conduction system during surgery can result in postoperative complete heart block. This complication is usually temporary and is treated with surgically placed pacing wires that can later be removed. Occasionally, complete heart block is permanent. If heart block persists beyond 10-14 days postoperatively, insertion of a permanent pacemaker is required. Tachyarrhythmias are a common problem in postoperative patients. Junctional ectopic tachycardia (JET) can be a particularly troublesome rhythm to manage, although it usually responds to antiarrhythmic medications such as intravenous amiodarone.

Heart failure with poor cardiac output after cardiac surgery may be secondary to respiratory failure, serious arrhythmias, myocardial injury, blood loss, hypovolemia, a significant residual hemodynamic abnormality, or any combination of these factors. Treatment specific to the cause should be instituted. Catecholamines, phosphodiesterase inhibitors, nitroprusside and other afterload-reducing agents, and diuretics are the cardioactive agents most often used in patients with myocardial dysfunction in the early postoperative period (see Chapter 491). Postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide (iNO). In the rare patients who are unresponsive to standard pharmacologic treatment, various ventricular assist devices are available, depending on the patient's size. If pulmonary function is adequate, a **left ventricular assist device (LVAD)** may be used. If pulmonary function is inadequate, **biventricular assist devices (BVAD)** or **extracorporeal membrane oxygenation (ECMO)** may be used. These extraordinary measures are helpful in maintaining the circulation until cardiac function improves, usually within 2-5 days. They have also been used as a bridge to transplantation in patients with severe nonremitting postoperative cardiac failure.

Acidosis secondary to low cardiac output, renal failure, or hypovolemia must be prevented or, if present, promptly corrected. Serial monitoring of arterial blood gases (ABGs) and lactate concentrations is performed. A low arterial pH may be a sign of decreased perfusion, and acidosis can worsen cardiac function and may be the forerunner of arrhythmias or cardiac arrest.

Renal function may be compromised by congestive heart failure and further impaired by prolonged CPB. Blood and fluid replacement, cardiac inotropic agents, and vasodilators will usually reestablish normal urine flow in patients with hypovolemia or cardiac failure. Renal failure secondary to tubular injury contributes to postoperative fluid overload and may require temporary peritoneal or hemodialysis or hemofiltration. With attention paid to renal injury during the perioperative period, the incidence and severity of chronic renal failure can be reduced.

Neurologic abnormalities can develop after CPB, especially in the neonatal period. Seizures may occur when the patient awakens from sedation and can usually be controlled with anticonvulsant medications. In the absence of other neurologic signs, self-limited isolated seizures in the immediate postoperative period usually carry a good long-term prognosis. Thromboembolism and stroke are rarer but serious complications of open heart surgery. In the long term, both subtle and more substantial learning disabilities may develop. Patients who have undergone surgery entailing CPB, especially in the newborn period, should be watched carefully during their early school years for signs of mild to moderate learning disabilities or attention deficit disorders, which are often amenable to early remedial intervention. The risk is higher in patients who have undergone repair using hypothermic total circulatory arrest than in those where systemic blood flow is maintained using CPB. With the increased recognition of the genetic link between CHD and moderate or greater neurodevelopmental delay, many of these cases may have multifactorial etiologies.

Postpericardiotomy syndrome may occur toward the end of the first postoperative week or may sometimes be delayed until weeks or months after surgery (Table 483.2). This febrile illness is characterized by fever, decreased appetite, listlessness, nausea, and vomiting. Chest pain is not always present, so a high index of suspicion should be maintained in any recently postoperative patient. Echocardiography is diagnostic. In most instances, postpericardiotomy syndrome is self-limited; when pericardial fluid accumulates rapidly, the potential danger of cardiac tamponade should be recognized (see Chapter 489).

Table 483.2 Postpericardiotomy Syndrome (PPS) Findings

FINDING	PERCENTAGE
SYMPTOMS	
Pleuritic or pericarditic chest pain	>50
Intermittent, low-grade fever	~50
CLINICAL FINDINGS	
Pericardial friction rub	20–30
Elevated C-reactive protein (CRP)	80–90
Elevated erythrocyte sedimentation rate (ESR)	80–90
Leukocytosis	80–90
Electrocardiogram (ECG): low voltage of the QRS, T-wave inversion, ST elevation or depression	~50
IMAGING	
Chest x-ray: pleural effusion	>90
Heart echocardiography: pericardial effusion	~90
Mild (<10 mm)	~75*
Moderate (10-20 mm)	~10*
Large (>20 mm)	~5
Pleuropericardial involvement	>80

*Of all PPS patients

From Lehto J, Kiviniemi T. Postpericardiotomy syndrome after cardiac surgery. *Ann Med.* 2020;52(6):243–264, Table 1.

Rarely, arrhythmias may also occur. Symptomatic patients usually respond to salicylates, indomethacin, or colchicine and bed rest. Occasionally, corticosteroid therapy or pericardiocentesis is required. Late recurrences are rare and can lead to chronic pericarditis.

Hemolysis of mechanical origin is seen, although rarely, after repair of certain cardiac defects, for example, atrioventricular septal defects (AVSDs), or after the insertion of a mechanical prosthetic valve. It is caused by unusual turbulence of blood at increased pressure. Reoperation may be necessary in rare patients with severe and progressive hemolysis who require frequent blood transfusions, but in most cases the problem slowly regresses.

Infection is another potentially serious postoperative problem. Patients usually receive a broad-spectrum antibiotic for the initial postoperative period. Potential sites of infection include the lungs (generally related to postoperative atelectasis), the subcutaneous tissues at the incision site, the sternum, and the urinary tract (especially after an indwelling catheter has been in place). Sepsis with infective endocarditis is an infrequent complication and can be difficult to manage, especially if prosthetic material was placed at surgery (see Chapter 486). Patients who undergo CPB during a viral infection, even if mild, can develop severe complications; therefore many anesthesiologists will postpone elective surgery if a child presents with a viral infection, either upper respiratory or gastrointestinal.

INTERSTAGE MANAGEMENT

One group of infants at particularly high risk for both morbidity and mortality are those who have completed their first-stage **Norwood** or **Sano** palliation for HLHS and are awaiting the next stage **(Glenn shunt)** of their three-stage palliation. Mortality in this group of infants had been reported as high as 10–15%, motivating the National Pediatric Cardiology Quality Improvement Collaborative **(NPC-QIC)** to develop an **interstage home monitoring program** that has been successful in reducing interstage mortality by 44%.

LONG-TERM MANAGEMENT

Patients who have undergone surgery for CHD can be divided into three major categories: lesions for which total repair has been achieved; lesions for which both anatomic and physiologic corrections have been achieved; and lesions for which only palliation, although potentially long term, has been achieved. There is some disagreement among cardiologists as to exactly in which category a particular congenital heart lesion might fall, and to some degree every case should be considered individually. Many argue that only for isolated patent ductus arteriosus (PDA) is total repair really achieved, with no requirement for long-term follow-up. Patients who are able to undergo anatomic and physiologic correction include many of the left-to-right shunt lesions (atrial and ventricular septal defects) and milder forms of obstructive lesions (e.g., valvar pulmonic stenosis, some forms of valvar aortic stenosis, coarctation of aorta) and some forms of cyanotic heart disease (e.g., uncomplicated tetralogy of Fallot, simple transposition of great arteries). These patients usually have achieved total or near-total physiologic correction of their lesion; however, they are still at some risk of long-term sequelae, including late heart failure or arrhythmia, or recurrence of a significant physiologic abnormality (e.g., recoarctation of aorta, worsening mitral regurgitation in patients with AVSDs, long-standing pulmonary regurgitation in patients with tetralogy of Fallot repaired with transannular patch). These patients require regular follow-up with a pediatric cardiologist (and, when old enough, with an **adult congenital heart disease specialist**; see Chapter 483.1); however, their long-term prognosis is generally very good, although some will require repeat surgeries or catheter-based interventions. Patients with more complex lesions, such as those with single-ventricle physiology (e.g., hypoplastic left or right heart syndrome), are at much higher risk of long-term sequelae and require even closer follow-up. These patients, particularly those who have undergone the Fontan procedure, are at risk long-term for arrhythmia, thrombosis, protein-losing enteropathy, plastic bronchitis, hepatic dysfunction (Fontan-associated liver disease or FALD), renal dysfunction, and heart failure. Some may eventually require heart, heart-liver, or heart-kidney transplantation.

Physical limitations in patients with CHD are variable, ranging from minimal to none in patients with physiologic correction to mild to moderate in patients with palliative procedures. The extent to which a patient should be allowed to participate in athletics, both recreational and competitive, can best be determined by the cardiologist, often with formal cardiopulmonary exercise testing (see Chapter 472.5).

Long-term morbidities affecting neurologic function and behavior are influenced by many factors, including the effects of any genetic alterations on the developing central nervous system (CNS). There may be a greater role for prenatal CNS abnormalities (anatomic, genetic, or secondary lesions caused by alterations in fetal cerebral blood flow or oxygenation); these include microcephaly, cerebral atrophy, and altered cerebral biochemistry. Chronic hypoxemia and failure to thrive may also influence the developing brain, and there is evidence that the type of intervention required (CPB, hypothermic total circulatory arrest, catheter-based therapy) plays a substantial role. Data from the **Pediatric Cardiac Genomics Consortium** have shown that there is also a genetic component to these learning disabilities. Performing exome sequencing on patients and their parents (trios), de novo gene variants were found in 2% of patients with CHD but in 20% of patients with CHD and neurodevelopmental delay. The identity of these gene variants and their mechanism of action is under study. In general, in the absence of a significant genetic syndrome or major perioperative complication, most children function at a fairly high level after repair of congenital heart defects and are able to attend regular school. Group mean scores on standard cognitive tests are no different from the general population; however, some areas appear to be more at risk than others, including certain aspects of motor function, speech, visual-motor tracking, and phonologic awareness. Awareness of these potential issues is critical to obtaining prompt remedial assistance if a child is found to be struggling in school.

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483.1 Congenital Heart Disease in Adults

Salil Ginde and Michael G. Earing

Approximately 90% of children with CHD survive to adulthood. More adults than children are living with CHD in the United States, with a 5% increase every year. In the past decade, 35% of hospitalizations for CHD were patients older than 18 years (mean age: 55 years).

LONG-TERM MEDICAL CONSIDERATIONS

Approximately 25% of adults with CHD have a mild form that has allowed them to survive into adulthood without surgical or interventional cardiac catheterization. The most common lesions in this category include mild aortic valve stenosis (usually in the setting of a bicuspid aortic valve), small restrictive ventricular septal defects (VSDs), mild pulmonary valve stenosis, and mitral valve prolapse (Table 483.3). These patients need less frequent follow-up to assess for progression of disease and to identify associated complications. Many adults with CHD living in the United States are patients who have had previous intervention (Table 483.4). Although most children who undergo surgical intervention will survive to adulthood, with few exceptions, *total correction is not the rule.* The few exceptions include PDA, VSDs, and atrial septal defects (ASDs); this is true only if they are closed early, before the development of irreversible pulmonary vascular changes, and if no residual lesions exist.

It has become apparent that even the simplest congenital heart lesions can be associated with long-term complications, including both cardiac and noncardiac problems (Tables 483.5 and 483.6 and Fig. 483.1). *Cardiac* complications include arrhythmias and conduction defects, ventricular dysfunction, residual shunts, valvular lesions (regurgitation and stenosis), hypertension, and aneurysms. *Noncardiac* sequelae **(comorbidities)** include pulmonary, renal, and hepatic dysfunction that is caused either directly or indirectly by the underlying CHD. Abnormal pulmonary function most often presents as restrictive lung physiology and likely results

Table 483.3 Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization

Mild pulmonary valve stenosis
Bicuspid aortic valve
Small to moderate-sized atrial septal defect
Small ventricular septal defect
Small patent ductus arteriosus
Mitral valve prolapse
Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve)
Marfan syndrome
Ebstein anomaly
Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)

Table 483.4 Most Common Congenital Heart Defects in Patients Surviving to Adulthood After Surgery or Interventional Catheterization

Aortic valve disease after balloon valvuloplasty or surgical valvotomy
Pulmonary valve stenosis after balloon valvuloplasty or surgical valvotomy
Tetralogy of Fallot
Ventricular septal defect
Complete atrioventricular canal defect
Transposition of the great arteries
Coarctation of the aorta
Complex single ventricles after the modified Fontan procedure

Table 483.5 Risks in Adults Who Have Congenital Heart Disease

RHYTHM DISORDERS
Supraventricular tachycardia (including atrial fibrillation)
Right bundle branch block
Heart block
Ventricular tachycardia
Sudden death
COARCTATION OF AORTA
Essential hypertension
Recoarctation
Aneurysm formation
RESIDUAL LESIONS (SHUNTS)
Ventral septal defect
Atrial septal defect
Patent ductus arteriosus
ACQUIRED LESIONS
Subacute bacterial endocarditis
Subvalvular stenosis
Supravalvular stenosis
Valvular insufficiency
Valvular restenosis
Eisenmenger complex
PREGNANCY RISK
See Figs. 483.2 and 483.3

Table 483.6 Adolescent Transition Issues Requiring Coordination of Patient Care Between the Cardiologist and Primary Care Physician

Antibiotic prophylaxis for endocarditis
Medications and drug interactions
Anticoagulation with prosthetic valves
Exercise and sports participation
Educational and vocational planning
Contraception and pregnancy
Drug, alcohol, and tobacco use
Noncardiac surgical planning
Anesthetic issues
New symptoms or acute illnesses
Comorbid conditions
Travel

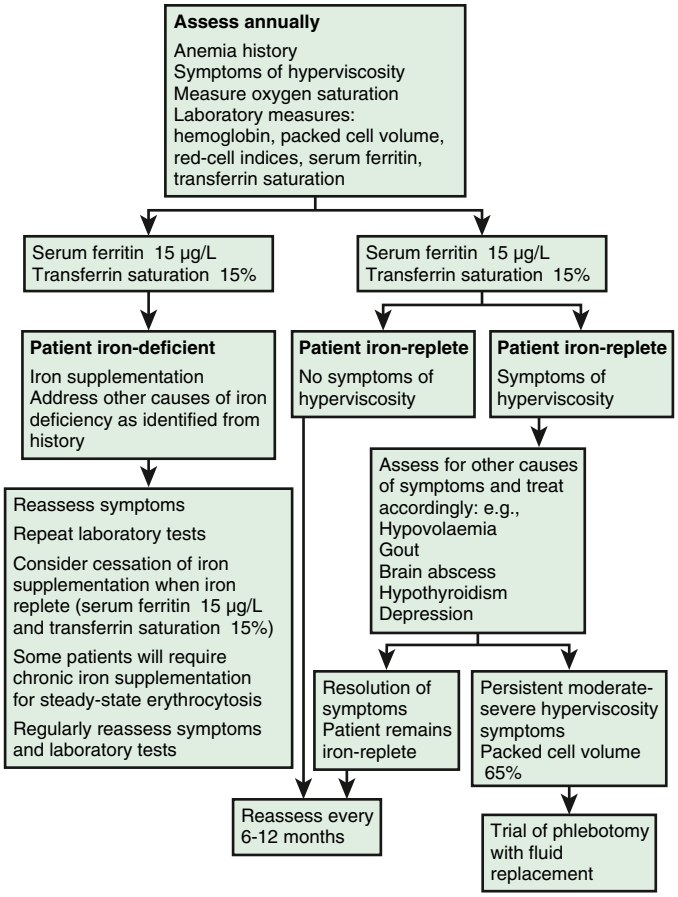


Fig. 483.1 Algorithm detailing crucial issues to address at transition to adulthood in patients with cyanotic congenital heart disease. *(From Spence MS, Balaratnam MS, Gatzoulis MA. Clinical update: cyanotic adult congenital heart disease. Lancet. 2007;370:1531.)*

from prior sternotomy or thoracotomy, scoliosis, diaphragmatic dysfunction, or parenchymal lung disease. Reduced pulmonary function contributes to reduced exercise tolerance and is a risk factor for mortality in adults with CHD. Renal dysfunction may result from chronic cyanosis, multiple surgeries requiring CPB, or from other comorbid conditions, such as hypertension and diabetes mellitus. Hepatic injury from chronic liver congestion in patients with elevated central venous pressures, particularly patients palliated with the Fontan procedure, can result in hepatic fibrosis, cirrhosis, hepatic dysfunction, and rarely, hepatocellular carcinoma. Adults with CHD are at risk for developmental abnormalities such as intellectual impairment, somatic abnormalities such as facial dysmorphism (cleft palate/lip), CNS abnormalities such as seizure disorders from previous thromboembolic events or cerebrovascular accidents, and impairments of hearing or vision loss. Psychosocial problems involving employment, life and health insurance, participation in sports, sexual activity, and contraception are common. Mental health issues, such as anxiety and depression, are common in adults with CHD and are often underrecognized and significantly affect quality of life. As a result of these long-term complications, the majority of adults with CHD need lifelong follow-up, ideally in an integrated, collaborative, and multidisciplinary program. When adults with CHD are hospitalized, it is usually for heart failure or an arrhythmia; others may require catheterization or another cardiac surgical procedure.

SPECIFIC LESIONS

Left-to-Right Shunts

In general, the long-term outcomes of adults with a history of shunt lesions that underwent repair early in life are good with near-normal life expectancy and relatively low risk for cardiac complications. However, if the initial lesion has a shunt that is large and nonrestrictive (allowing transmission of near-systemic pressure to the pulmonary arteries) and is unrepaired, irreversible pulmonary vascular changes can occur, resulting in pulmonary hypertension at systemic levels with reversed or bidirectional shunting at the level of the defect (**Eisenmenger syndrome**; see Chapter 482.2).

Atrial Septal Defects

See Chapter 475.1.

Although most individuals with an ASD are diagnosed during childhood after a murmur is noted, a minority of patients present with symptoms for the first time as adults. Most patients are asymptomatic during the first and second decades of life. In the third decade, an increasing number of patients then develop exercise intolerance, palpitations from atrial arrhythmias, and cardiac enlargement. If untreated, survival into adulthood is the rule; life expectancy is reduced, however, and there is significant long-term morbidity. After age 40 the mortality rate increases by 6% per year, and >20% of patients will have developed atrial fibrillation (AF). By age 60 the number of patients with AF increases to >60%.

Late Outcome After Closure of Atrial Septal Defect

Most patients who have undergone early ASD closure will have excellent long-term survival with low morbidity if repair is undertaken before age 25 years. Older age at repair is associated with decreased late survival with an associated increased risk for the development of atrial arrhythmias, thromboembolic events, and pulmonary hypertension. Long-term late complications and survival after transcatheter device closure remain unknown; early and intermediate results are excellent, with a high rate of ASD closure and few major complications.

Ventricular Septal Defects

See Chapter 475.6.

Although isolated VSDs are among the most common forms of CHD, the diagnosis of a VSD in an adult is rare. The primary reason is that most patients with a hemodynamically significant VSD will have undergone repair in childhood or will have died earlier in life. As result, the spectrum of isolated VSD in adults is limited to (1) those with small restrictive defects, (2) those with Eisenmenger syndrome, and (3) those who had their defects closed in childhood.

For patients with **small restrictive VSD**, long-term survival is excellent, with estimated 25-year survival of 96%. In addition, the long-term morbidity for patients with a restrictive VSD also appears to be low. Their clinical course is not completely benign. Reported long-term complications include endocarditis, progressive aortic regurgitation secondary to prolapse of the aortic valve into the defect (highest risk is with supracristal type but also can occur in setting of perimembranous defect), and the development of both right and left outflow tract obstruction from a double-chamber RV or a subaortic membrane. For patients who develop **Eisenmenger syndrome**, survival into the third decade is common. With increasing age, the long-term complications of right-sided heart failure, paradoxical emboli, and polycythemia usually result in progressive decline in survival, with death at an average age of 37 years.

Adults with **previous VSD closure**, without pulmonary hypertension or residual defects, live a normal life expectancy. Because patients with small VSDs are asymptomatic, these patients should be managed conservatively. Given the long-term risks, they do need intermittent follow-up for life to monitor for the development of late complications. The exception to this rule is patients with small supracristal or perimembranous VSD with associated prolapse of the aortic cusp into the defect resulting in progressive aortic regurgitation. These patients should be considered for surgical repair at diagnosis to prevent progressive aortic valve damage.

Complete Atrioventricular Canal

See Chapter 475.5.

The natural history for patients with complete AVSD is characterized by the early development of pulmonary vascular disease, leading to irreversible damage often by age 1 year (especially in children with Down syndrome). Thus patients who present in adulthood can be categorized into two groups: those with Eisenmenger syndrome and those who had their defects closed in childhood.

Overall, for those patients who underwent early repair before the development of pulmonary vascular disease, the long-term prognosis is good. The most common long-term complication is **left atrioventricular valve regurgitation**, with approximately 5–10% of patients requiring surgical revision for left atrioventricular valve repair or replacement during follow-up. The second most common long-term complication for this patient group is **subaortic stenosis**, occurring in up to 5% of patients after repair. Other long-term complications include residual atrial- or ventricular-level shunts, complete heart block, atrial and ventricular arrhythmias, and endocarditis.

For patients who have developed Eisenmenger syndrome, all are symptomatic with exertional dyspnea, fatigue, palpitations, edema, and syncope. Survival is similar to other forms of Eisenmenger syndrome, with a mean age at death of 37 years. Strong predictors for death include syncope, age at presentation of symptoms, poor functional class, low oxygen saturation (<85%), elevated serum creatinine and uric acid concentrations, and Down syndrome.

Patients who underwent previous repair and develop significant left atrioventricular valve regurgitation causing symptoms, atrial arrhythmias, or deterioration in ventricular function should undergo elective valve repair or replacement. Those previously repaired patients who develop significant subaortic stenosis (defined as a peak cardiac catheterization or echo gradient of >50 mm Hg) should undergo surgical repair.

Patent Ductus Arteriosus

See Chapter 475.8.

A PDA is usually an isolated lesion in the adult patient. The size of the defect is the primary determinant of clinical course in the adult patient. These clinical courses can be grouped into five main categories: silent PDAs; small, hemodynamically insignificant PDAs; moderate-size PDAs; large PDAs; and previously repaired PDAs.

A **silent** PDA is a tiny defect that cannot be heard by auscultation and is only detected by other means such as echocardiography. Life expectancy is always normal in this population, and the risk for endocarditis is extremely low.

Patients with a **small** PDA have an audible long-ejection or continuous murmur heard best at the left upper sternal border that radiates to the back. In addition, they have normal peripheral pulses. Because there is negligible left-to-right shunting these patients have normal left atrial and left ventricle (LV) size and normal pulmonary artery pressure by echocardiography and chest x-ray film. These patients, like those with silent PDAs, are asymptomatic and live a normal life expectancy. They have a higher risk for endocarditis.

Patients with **moderate-size** PDAs may present during adulthood. These patients often will have wide, bounding peripheral pulses and an audible continuous murmur. These patients all have significant volume overload and develop some degree of left atrial and LV enlargement and some degree of pulmonary hypertension. These patients are symptomatic with dyspnea, palpitations, and heart failure.

Patients with **large** PDAs typically present with signs of severe pulmonary hypertension and Eisenmenger syndrome. By adulthood, the continuous murmur is typically absent and there is differential cyanosis (lower-extremity saturations lower than the right arm saturation). These patients have a similar prognosis as other patients with Eisenmenger syndrome.

Patients who underwent **repair** of a PDA before the development of pulmonary hypertension have a normal life expectancy without restrictions.

All patients with *clinical evidence* of a PDA are at increased risk for endocarditis. As result, all PDAs except for small silent PDAs and those patients with severe irreversible pulmonary hypertension should be considered for closure. Catheter device closure is the preferred method in most centers today. Surgical closure is reserved for patients with PDA too large for device closure or when the anatomy is distorted, as in the setting of a large ductal aneurysm.

Cyanotic Heart Disease

See Chapters 478, 479, and 480.

Unlike the acyanotic forms of CHD, the majority of patients with cyanotic CHD will have had at least one and often several previous interventions before adulthood. The most frequent defects seen in the outpatient adult CHD setting are tetralogy of Fallot, complete transposition of the great arteries (TGA, also known as *d-transposition*), pulmonary valve stenosis, and various forms of functional single ventricles. Other defects include total anomalous pulmonary venous return, truncus arteriosus, and double-outlet RV.

Tetralogy of Fallot

See Chapter 479.1.

In the developed world, the unoperated adult patient with tetralogy of Fallot is a rarity because the majority of patients will have undergone palliation or, more often, repair in childhood. Only 11% of unoperated patients are alive by age 20 and only 3% by age 40.

Late survival after repair of tetralogy of Fallot is excellent. Repair is typically performed at 3-12 months of age and consists of patch closure of the VSD and relief of the pulmonary outflow tract obstruction by patch augmentation of the right ventricular outflow tract, pulmonary valve annulus, or both. Survival rates at age 32 and 35 years have been reported to be 86% and 85%, respectively, compared with 95% in age- and sex-matched controls. Most patients live an unrestricted life. Many patients do develop late symptoms that include exertional dyspnea, palpitations, syncope, and sudden cardiac death. Late complications include endocarditis, aortic regurgitation with or without aortic root dilation (typically caused by damage to the aortic valve during VSD closure or secondary to an intrinsic aortic root abnormality), left ventricular dysfunction (secondary to inadequate myocardial protection during previous repair or chronic LV volume overload caused by long-standing palliative arterial shunts), residual pulmonary valve obstruction, residual pulmonary valve regurgitation, RV dysfunction (as a result of pulmonary regurgitation or pulmonary stenosis), atrial arrhythmias (typically atrial flutter), ventricular arrhythmias, and heart block.

Reintervention is necessary in approximately 10% of patients after reparative surgery at 20-year follow-up. With longer follow-up, the incidence of reintervention continues to increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary valve regurgitation. Pulmonary valve replacement, either surgical or transcatheter, is indicated when severe pulmonary valve regurgitation is associated with RV or LV systolic dysfunction, severe RV dilation, and/or progressive reduction in objective exercise tolerance. Although pulmonary valve replacement is associated with improved functional status, it has not been shown to improve mortality or risk for ventricular arrhythmias and sudden cardiac death in adults with tetralogy of Fallot. Implantable cardioverter defibrillators may be considered in patients with a history of recurrent ventricular arrhythmias or other risk factors such as ventricular dysfunction.

Transposition of the Great Arteries

See Chapter 480.1.

The natural history of patients with unrepaired TGA is so poor that very few patients survive past childhood without intervention. The first definitive operations for TGA was the **atrial switch** procedure, where the systemic and pulmonary venous returns are rerouted in the atrium by constructing baffles. The systemic venous return from the superior and inferior venae cavae is directed through the mitral valve and into the left ventricle (connected to the pulmonary artery). The pulmonary venous return is then directed through the tricuspid valve into the RV (connected to the aorta). The procedure results in physiologic correction and can be performed with low mortality but leave the left as the pulmonary ventricle and the right as the systemic ventricle. Long-term follow-up studies after the *atrial switch* procedure show a small but ongoing attrition rate with numerous other intermediate- and long-term complications. Two specific problems are most concerning: loss of sinus rhythm with development of atrial arrhythmias, occurring in 50% of TGA patients by age 25, and development of systemic ventricular dysfunction, occurring in 50% by age 35. Other long-term complications include endocarditis, baffle leaks, baffle obstruction, tricuspid valve regurgitation, and sinus node dysfunction requiring pacemaker placement.

The **arterial switch** operation is the procedure of choice to treat TGA. The great arteries are transected and reanastomosed to the correct ventricle (LV to aorta, RV to pulmonary artery) with coronary artery transfer. Operative survival after the arterial switch procedure in the current surgical era is very good, with a surgical mortality rate of 2–5%. Long-term data on survival and complications are not available, but intermediate results are promising. Reported intermediate complications include endocarditis, pulmonary outflow tract obstruction (at the supravalvular level or at the takeoff of the peripheral pulmonary arteries), aortic valve regurgitation, and coronary artery compromise (ranging from minor stenosis to complete occlusion).

The **Rastelli operation** represents a third type of repair for TGA, typically when there is associated VSD and pulmonary outflow tract obstruction. This operation involves the creation of an intracardiac baffle that closes the VSD in a way that directs flow from the LV to the aorta. The pulmonary valve is oversewn, and a valved conduit placed between the RV and pulmonary artery. Operative mortality is low, but patients require multiple reoperations for replacement of the pulmonary conduit during long-term follow-up. Other complications include complete heart block and left ventricular outflow tract obstruction.

Because of the high incidence of observed and potential medical problems, all patients who have had atrial, arterial, or Rastelli repair of TGA should have lifelong follow-up by a cardiologist at a center specializing in adult CHD.

Pulmonary Valve Stenosis

See Chapter 476.1.

Most patients with pulmonary valve stenosis are asymptomatic and present with a cardiac murmur. Survival into adult life and the need for intervention, however, are directly correlated to the degree of obstruction. Patients with **trivial** stenosis (defined as a peak gradient <25 mm Hg) followed for 25 years remain asymptomatic and have no significant progression of obstruction over time. For those patients with **moderate** pulmonary valve stenosis (defined as a peak gradient of 25-49 mm Hg), there is an approximately 20% chance of requiring intervention by age 25. For those patients with severe stenosis (defined as a peak gradient >50 mm Hg), the majority ultimately require an intervention, either surgery or balloon valvuloplasty, by age 25.

After surgical valvotomy for isolated pulmonary stenosis, long-term survival is excellent. With longer follow-up, the incidence of late complications and the need for reintervention do increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary regurgitation. Other long-term complications include recurrent atrial arrhythmias, endocarditis, and residual right ventricular outflow tract obstruction.

Patients with **moderate to severe** pulmonary stenosis (defined as a peak gradient >50 mm Hg) should be considered for intervention even in the absence of symptoms. Percutaneous balloon valvuloplasty has been the accepted treatment for patients of all ages. Previously, surgical valvotomy had been the gold standard. Surgical valvotomy is reserved for patients who are unlikely to have successful results from balloon valvuloplasty, such as those with an extremely dysplastic or calcified valve.

Left-Sided Obstructive Lesions

Coarctation of the Aorta

See Chapter 476.6.

The clinical presentation of coarctation of the aorta depends on the severity of obstruction and the associated anomalies. Unrepaired coarctation typically presents with symptoms before adulthood. These symptoms include headaches related to hypertension, leg fatigue or cramps, exercise intolerance, and systemic hypertension (may be asymptomatic). Those untreated patients surviving to adulthood thus typically have only mild coarctation of the aorta. In the era before surgery, without treatment, the mean age of death was 32 years. Causes of death included left ventricular failure, intracranial hemorrhage, endocarditis, aortic rupture/dissection, and premature coronary artery disease (CAD).

After surgical repair, long-term survival is good but is directly correlated with the age at repair, with those repaired after age 14 years having a lower 20-year survival than those who were repaired earlier: 91% vs 79%. With longer follow-up, the incidence of long-term complications

continues to rise. The most common long-term complication is persistent or new systemic hypertension at rest or during exercise. Other long-term complications include aneurysms of the ascending or descending aorta, recoarctation at the site of previous repair, CAD, aortic stenosis or regurgitation (in the setting of an associated bicuspid aortic valve), rupture of an intracranial aneurysm, and endocarditis.

Patients with significant native or residual coarctation of the aorta (symptomatic patients with a peak gradient across the coarctation >20 mm Hg) should be considered for intervention, either surgery or catheter intervention with balloon angioplasty, with or without stent placement. Surgical repair in the adult patient is technically difficult and is associated with high morbidity. Catheter-based intervention is the preferred method in most experienced adult CHD centers.

Aortic Valve Stenosis

See Chapter 476.5.

The natural history of aortic valve stenosis in adults is quite variable but is characterized by progressive stenosis over time. By age 45 years, approximately 50% of bicuspid aortic valves will have some degree of stenosis.

Most patients with aortic valve stenosis are asymptomatic and are diagnosed after a murmur is detected. The severity of obstruction at diagnosis correlates with the pattern of progression. Symptoms are rare until patients have severe aortic valve stenosis (mean gradient by echocardiography >40 mm Hg). Symptoms include chest pain, exertional dyspnea, near-syncope, and syncope. When any of these symptoms is present, the risk of sudden cardiac death is quite high, so surgical intervention is mandated. For patients requiring surgical valvotomy to relieve the stenosis before adulthood, the majority of patients do well. However, at 25-year follow-up, up to 40% of patients will have required a second operation for residual stenosis or regurgitation.

Patients with symptoms and severe aortic valve stenosis should be considered for intervention. Treatment involves manipulating the valve to reduce stenosis. This can be accomplished by balloon dilation of the valve, open surgical valvotomy, or valve replacement. In absence of significant aortic regurgitation, most centers favor balloon dilation or surgical valvotomy for children and young adults who have pliable valves with fusion of commissures. In older adults, aortic valve replacement is the treatment of choice. Typically, surgery is performed for aortic valve replacement in younger adults with congenital aortic valve stenosis; however, transcatheter aortic valve replacement is increasingly commonly performed in older adults who may be higher-risk surgical candidates.

Endocarditis Prophylaxis

See Chapter 486.

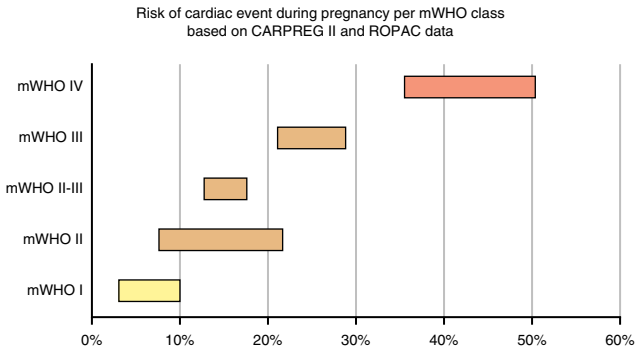
Only patients with cardiac conditions associated with the highest risk for adverse outcomes should continue antibiotic prophylaxis before surgery: previous endocarditis, prosthetic valves (biological and mechanical), unrepaired cyanotic CHD, including palliative shunts and conduits, completely repaired congenital heart defects with prosthetic material or device, surgically placed or by catheter intervention during the first 6 months after the procedure, and repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). Except for the conditions just listed, antibiotic prophylaxis is no longer recommended for other forms of CHD.

PREGNANCY AND CONGENITAL HEART DISEASE

CHD is the most common form of heart disease encountered during pregnancy in developed countries. Heart disease does not preclude a successful pregnancy but increases the risk to both the mother and the baby. During pregnancy, substantial hemodynamic changes occur. The hemodynamic changes in pregnancy result in a steady increase in cardiac output during pregnancy until the 32nd week of gestation, at which time the cardiac output reaches a plateau at 30–50% above the prepregnancy level. At delivery, with uterine contractions, an additional 300-500 mL of blood enters the circulation. This, in conjunction with increased blood pressure and heart rate during labor, increases the cardiac output at delivery to 80% of the prepregnancy level.

Despite these hemodynamic changes, the outcome of pregnancy is favorable in most women with CHD, provided that functional class and systemic ventricular function are good. The WHO modified categorization of risk stratification is shown in Figures 483.2 and 483.3. Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, regardless of functional class. Other contraindications to pregnancy include severe obstructive left-sided lesions (coarctation of the aorta, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy), Marfan syndrome with coexisting dilated ascending aorta (defined as >4 cm), persistent cyanosis, and systemic ventricular dysfunction (ejection fraction of ≤40%). The need for full anticoagulation during pregnancy, although not a contraindication, poses an increased risk to both mother and fetus. The relative risks and benefits of the different anticoagulant approaches need to be discussed fully with the mother.

Pregnancy counseling should begin early in adolescence and should be part of the routine cardiac follow-up visit. Counseling should include a discussion about the risk of CHD in the offspring. In the general population, the incidence of CHD is 1%. In the offspring of a mother with CHD, the risk increases to 5–6%. Often the cardiac lesion in the offspring is not the same as that in the mother, except in the case of a syndrome with autosomal dominant inheritance (i.e., Marfan syndrome, hypertrophic cardiomyopathy). Risk stratification should include the specific CHD lesion but also needs to consider the maternal functional class. Although the specific CHD lesion is important, multiple studies demonstrate that the maternal functional class before pregnancy is highly predictive of both maternal and fetal outcomes, with those in the best functional class having the best outcomes. A cardiopulmonary exercise test performed before conception can predict maternal and neonatal outcomes in pregnant women with CHD. A blunted heart rate response to exercise is associated with a higher risk for adverse maternal and neonatal events. It is recommended that women with CHD at higher risk for pregnancy-related complications based on anatomy, functional status, and exercise testing be managed collaboratively during pregnancy by adult CHD cardiologists, obstetricians, and anesthesiologists with specialized experience in adults with CHD.



	Predictors of cardiac event during pregnancy	OR in study cohort	Event rate in study cohort
CARPREG II	Prior cardiac event or arrhythmia	5.9	33%
	NYHA III or IV or cyanosis	4.9	46%
	Mechanical valve	4.2	38%
	Ventricular dysfunction	2.3	30%
	High risk left-sided valve disease/left ventricular outflow tract obstruction	2.1	22%
	Pulmonary hypertension	3.3	32%
	Coronary artery disease	3.0	29%
	High risk aortopathy	2.7	18%
	No prior cardiac intervention	1.6	18%
	Late pregnancy assessment	1.6	20%
ZAHARA	Cardiac medication, other than anticoagulation	4.2	26%
	Atrioventricular valve regurgitation	2.0–2.3	17%
ROPAC	Atrial fibrillation at pre-pregnancy visit	5.1	52%
	Signs of heart failure at pre-pregnancy visit	3.3–4.2	63%

Fig. 483.2 Risk tools modified WHO (mWHO), CARdiac disease in PREGnancy (CARPREG), Zwangerschap bij Aangeboren HARtAfwijking (ZAHARA), Registry of Pregnancy and Cardiac disease (ROPAC). ORs and rates are derived from cohorts consisting of approximately 60% of patients with congenital heart disease (63% in CARPREG II and 58% in ROPAC). OR, Odds ratio. *(From van Hagen IM, Roos-Hesselink JW. Pregnancy in congenital heart disease: risk prediction and counselling. Heart. 2020;106:1853–1861, Fig. 1.)*

CONTRACEPTION

A critical part of caring for adults with CHD is to provide (or make available) advice on contraception. Unfortunately, data are limited on the safety of various contraceptive techniques in adult CHD patients. The estrogen-containing oral contraceptives (OCs) can be used in many adult CHD patients but are not recommended in adult CHD patients at risk for thromboembolism, such as those with cyanosis, prior Fontan procedure, AF, or pulmonary artery hypertension. In addition, OCs may disrupt anticoagulation control. Although slightly less effective than OCs containing combined estrogen/progesterone, medroxyprogesterone, the progesterone-only pills, and levonorgestrel are good options for most adult CHD patients. Medroxyprogesterone and levonorgestrel, however, can cause fluid retention and thus need to be used with caution in patients with heart failure. These medications are also associated with depression and often breakthrough bleeding. Tubal ligation, although the most secure method of contraception, can be a high-risk procedure in patients with complex CHD or those with pulmonary hypertension. Hysteroscopic sterilization (Essure) may be reasonable for high-risk patients. In the past, intrauterine devices (IUDs) were seldom used in cardiac patients because of the associated risk of bacteremia, pelvic inflammatory disease, and endocarditis. IUDs such as Mirena appear to be safe and effective and are rapidly becoming one of the most common forms of contraception in the adult CHD population.

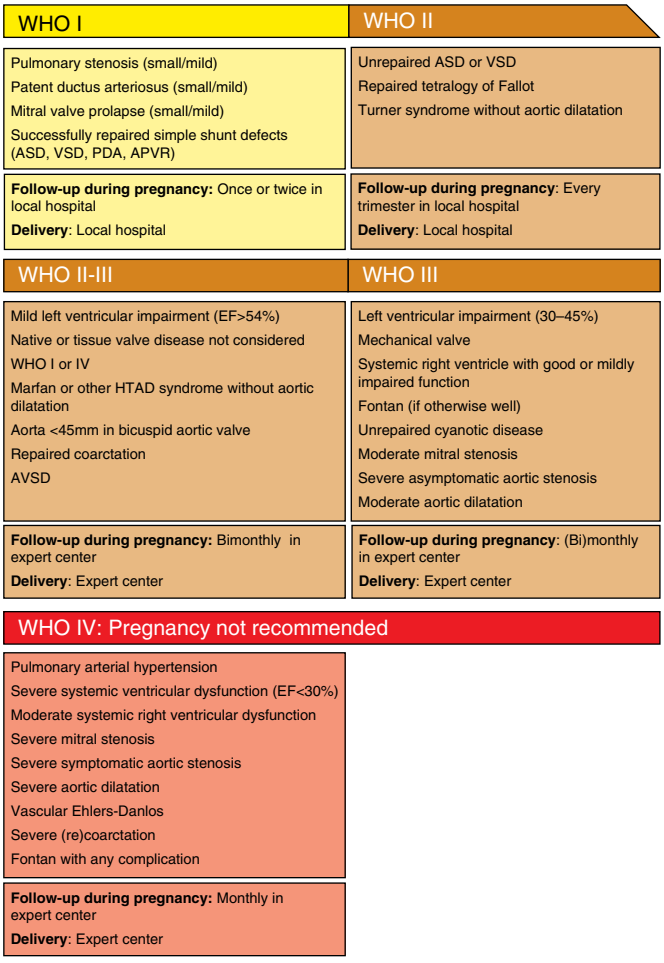


Fig. 483.3 Advised counseling for pregnancy in congenital heart disease. APVR, Anomalous pulmonary venous return; ASD, atrial septal defect; AVSD, atrioventricular septal defect; EF, ejection fraction; ESC, European Society of Cardiology; HTAD, hereditary thoracic aorta disease; PDA, persistent ductus arteriosus; VSD, ventricular septal defect; WHO, World Health Organization. *(From van Hagen IM, Roos-Hesselink JW. Pregnancy in congenital heart disease: risk prediction and counselling. Heart. 2020;106:1853–1861, Fig. 2.)*

ADOLESCENT TRANSITION

It is well recognized that as part of the process of obtaining independence, adolescents or young adults must develop a forward-looking, independent approach to their medical care. For children with heart disease, the transition process must begin during early adolescence and should be encouraged by both the primary care provider and the pediatric cardiologist, who must identify an appropriate adult CHD program to which transition and transfer will be made at an appropriate time (see Table 483.6).

A successful transition program includes the following elements:

- Development of a written transition plan that should begin by age 14 years
- Because adolescents and young adults are frequently unaware of the details of their cardiac diagnosis and history, a complete, concise, portable medical record, including all pertinent aspects of cardiac care, should be shared with adolescents and their family and prepared for transmittal to the eventual adult care destination.
- The primary care provider and cardiologist must address unique adolescent medical issues as they affect the cardiovascular system. In addition to medical problems, education, vocational planning, psychosocial issues, and access to medical care should be discussed with adolescents and their families.

Young adults tend to avoid medical care because of lack of education, denial, or difficulty with access to the medical care system. Thus a critical goal of the adolescent transition process is to identify an appropriate site for ongoing medical care and ensure maintenance of the medical record and continuity of care for the young adult. The site of care for a young adult with CHD may be a pediatric program or facility or a specialized center or program for the adult with CHD. The critical issues are the continuity of care, the preparation of the patient, and the patient's participation in the process.

HEART FAILURE AND TRANSPLANT

Heart failure is increasingly prevalent in adults with CHD and is associated with increased morbidity and mortality. Causes for heart failure in this population include unrepaired or residual valve dysfunction, shunts, arrhythmias, venous obstruction, and systolic and/or diastolic ventricular dysfunction. Data on medical and device therapy to treat heart failure in adults with CHD are limited because of the relatively small study populations and heterogenous heart defects. Concomitant failure of noncardiac organs, such as lung, kidney, and liver failure, is common in adult CHD patients with heart failure and further complicates the management. Currently, management of symptomatic CHD patients with systolic ventricular dysfunction is primarily extrapolated from data in adults with heart failure in the setting of acquired heart disease and includes:

- Medical therapy that includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, aldosterone antagonists, and diuretics
- Electrical device therapies such as implantable cardioverter defibrillators to reduce the risk for sudden cardiac death and permanent pacemaker placement for cardiac resynchronization therapy to improve symptoms of heart failure
- Mechanical circulatory support, such as ventricular assist devices, for patients with severe, refractory heart failure symptoms
- Referral to adult CHD heart failure/transplant specialist and center

Proper timing for heart transplantation in adults with CHD is unclear and may vary for individual lesions. Patients with single ventricle anatomy and complex anatomy often have lower priority with the current transplant allocation system, and therefore often have longer wait times before receiving a heart transplant. Early posttransplant mortality is higher in adults with CHD compared with adults with acquired heart disease because of increased perioperative mortality. However, once beyond the perioperative period, patients with ACHD do as well as or better than those with acquired heart disease, with expected 10-year survival equivalent to or better than that of adults without CHD.

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Section 4

Cardiac Arrhythmias

Chapter 484

Disturbances of Rate and Rhythm of the Heart

Aarti S. Dalal and George F. Van Hare

The term *arrhythmia* refers to a disturbance in heart rate or rhythm. Such disturbances can lead to heart rates that are abnormally fast, slow, or irregular. They may be transient or incessant; congenital or acquired; or caused by infection, a toxin, or drugs. They may be associated with particular forms of congenital heart disease (CHD), may be a complication after surgical repair of CHD, may be a result of genetic causes, or may be the result of a maternal connective tissue disease. Arrhythmias, either slow or fast, may lead to acutely decreased cardiac output. If incessant, they may lead to a cardiomyopathy. Initially stable and organized arrhythmias can degenerate into a more dangerous arrhythmia such as ventricular fibrillation. Arrhythmias may lead to syncope or to sudden death (see Chapter 485). When a patient has an arrhythmia, it is important to determine whether the rhythm is likely to lead to symptoms or to deteriorate into a life-threatening condition. Rhythm abnormalities such as single premature atrial and ventricular beats are common, and in children without heart disease, usually pose no risk to the patient.

A number of **pharmacologic agents** are available for treating arrhythmias; many have not been studied extensively in children. Insufficient data are available regarding pharmacokinetics, pharmacodynamics, and efficacy in the pediatric population, and therefore the selection of an appropriate agent is based on the judgement and experience of the clinician. Fortunately, most rhythm disturbances in children can be reliably controlled with a single agent (Table 484.1). **Transcatheter ablation** is acceptable therapy not only for life-threatening or drug-resistant arrhythmias but also for the cure of arrhythmias. For patients with bradycardia, **implantable pacemakers** are small enough for use in all ages, even in premature infants. Implantable cardioverter-defibrillators are available for use in high-risk patients with malignant ventricular arrhythmias and an increased risk of sudden death.

484.1 Principles of Antiarrhythmic Therapy

Aarti S. Dalal and George F. Van Hare

Many antiarrhythmic agents are available for rhythm control. The majority are not approved by the U.S. Food and Drug Administration (FDA) for use in children; their use is therefore considered "off-label." Pediatric cardiologists have experience with these drugs, with well-recognized standards for dosing.

With the availability of potentially curative ablation procedures, medical therapy has become less important. Intolerable drug side effects, as well as the potential for an arrhythmia induced by an antiarrhythmic drug, can seriously limit medical therapy and will lead the physician and family toward a potentially curative ablation procedure.

Antiarrhythmic drugs are frequently categorized using the **Vaughan-Williams classification**. This system comprises four classes: **class I** includes agents that primarily block the sodium channel, **class II** drugs are the β blockers, **class III** includes agents that prolong repolarization by blocking potassium channels, and **class IV** drugs are the calcium channel blockers. Class I is further divided by the strength of the sodium channel blockade (see Table 484.1).

484.2 Sinus Arrhythmias and Extrasystoles

Aarti S. Dalal and George F. Van Hare

Phasic sinus arrhythmia represents a normal physiologic variation in impulse discharges from the sinus node related to respirations. The heart rate slows during expiration and accelerates during inspiration. Occasionally, if the sinus rate becomes slow enough, an **escape beat** arises from the atrioventricular (AV) junction region (Fig. 484.1). Normal phasic sinus arrhythmia is caused by the activity of the parasympathetic nervous system and can be quite prominent in healthy children. It may mimic frequent premature contractions, but the relationship to the phases of respiration can be appreciated with careful auscultation. Drugs that increase vagal tone, such as digoxin, may exaggerate sinus arrhythmia; it is usually abolished by exercise. Other irregularities in sinus rhythm, especially bradycardia associated with periodic apnea, are common in premature infants.

Sinus bradycardia is a result of slow discharge of impulses from the sinus node, the heart's "natural pacemaker." A sinus rate <90 beats/min in neonates and <60 beats/min in older children is considered sinus bradycardia. Sinus bradycardia is commonly seen in highly conditioned athletes. In healthy individuals without symptoms, it has no clinical significance. Sinus bradycardia may occur in systemic disease (hypothyroidism, anorexia nervosa), and it resolves when the disorder is under control. It may also be seen in association with conditions in which there is high vagal tone, such as gastrointestinal obstruction or intracranial processes. Low birthweight infants display great variation in sinus rate. Sinus bradycardia is common in these infants, in conjunction with apnea, and may be associated with junctional escape beats; premature atrial contractions are also frequent. These rhythm changes, especially bradycardia, appear more often during sleep and are not associated with symptoms. Usually, no therapy is necessary.

A **wandering atrial pacemaker** is defined as an intermittent shift in the pacemaker of the heart from the sinus node to another part of the atrium. It is not uncommon in childhood and usually represents a normal variant. It may also be seen in association with sinus bradycardia in which the shift in atrial focus is an escape phenomenon.

Extrasystoles are produced by the premature discharge of an ectopic focus that may be situated in the atrium, the AV junction, or the ventricle. Usually, isolated extrasystoles are of no clinical or prognostic significance. Under certain circumstances, however, premature beats may be caused by organic heart disease (inflammation, ischemia, fibrosis) or drug toxicity.

Atrial extrasystoles, also known as **premature atrial contractions** or **complexes (PACs)**, are common in childhood, usually in the absence of cardiac disease. Depending on the degree of prematurity of the beat (coupling interval) and the preceding R-R interval (cycle length), PACs may result in a normal, a prolonged (aberrancy), or an absent (blocked PAC) QRS complex. Blocked PACs occur when the premature impulse cannot conduct to the ventricle because of refractoriness of the AV node or distal conducting system (Fig. 484.2). Atrial extrasystoles must be distinguished from premature ventricular contractions. Careful scrutiny of the electrocardiogram (ECG) for a premature P wave preceding the QRS will show either a premature P wave superimposed on and deforming the preceding T wave or a P wave that is premature and has a different contour from that of the other sinus P waves. PACs usually reset the sinus node pacemaker, leading to an incomplete compensatory pause, but this feature is not always present and so is not regarded as a completely reliable means of differentiating atrial from ventricular premature complexes in children.

Ventricular extrasystoles, also known as **premature ventricular contractions** or **complexes (PVCs)**, may arise in any region of either ventricle. PVCs are characterized by premature, widened, bizarre QRS complexes that are not preceded by a premature P wave (Fig. 484.3). When all premature beats have identical contours, they are classified

Table 484.1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS NA^+ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT; in atrial flutter, an AV node–blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1:1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) 200 mg q6 (1-1.5 g/day divided q6), sulfate; 324 mg q8-12h (1.5 g/day divided q8-12h), gluconate Max dose: 2.4 g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole, syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/day divided q3-6h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-60 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral (immediate release): <1 yr: 10-30 mg/kg/day divided q6h 1-4 yr: 10-20 mg/kg/day divided q6h >4-12 yr: 10-15 mg/kg/day divided q6h >12- ≤18 yr: 6-15 mg/kg/day divided q6h Max dose: 1.6 g/day Adults: <50 kg: 100 mg q6h; >50kg:150 mg q6h Long-acting dosing is 200-300 q12h	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-7 µg/mL
CLASS IB: INHIBITS NA^+ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg) Adult infusion rate: 1-4 mg/min	CNS effects, confusion, convulsions, high-grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1.5-5.0 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h Max dose: 15 mg/kg/day or 1.2 g/day. Adults: 150-300 mg q8-12h (max 1.2 g/day)	GI upset, skin rash, neurologic	Cimetidine	0.5-2 mcg/mL
Phenytoin	Digitalis intoxication	Oral: 4-8 mg/kg/24 hr divided q12h Max dose: 300-600 mg/day IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS NA^+ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	BSA dosing: 50-200 mg/m^2/day divided q8-12h Weight based: 3-6 mg/kg/day divided q8h Max dosing: 8 mg/kg/day Max adult dosing: 400 mg/day	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL

Table 484.1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class—cont'd

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m^2/24 hr divided q8h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 μg/mL
CLASS II: β BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.01-0.15 mg/kg/dose SLOW over 5-10 min Max dose: 1-3 mg/dose	Bradycardia, loss of concentration, school performance problems, bronchospasm, hypoglycemia, hypotension, heart block, CHF	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24 hr given once daily	Bradycardia, loss of concentration, school performance problems, bronchospasm, hypoglycemia, hypotension, heart block, CHF	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10-15 mg/kg/day IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 5-20 mg/kg/day continuous infusion Max daily dose: 2.2 g/day	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	1-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 μg/kg Newborn: 30 μg/kg >6 mo: 40 μg/kg Give 1/2 total dose followed by 1/4 q8-12h × 2 doses Maintenance: 10 μg/kg/24 hr divide q12h Max dose: 0.5 mg IV: 3/4 PO dose Max dose: 0.5 mg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
Verapamil	SVT (not WPW)	Oral: 2-8 mg/kg/day divided q8h Max dose: 480 mg/day IV: 0.1-0.3 mg/kg/dose Max dose: 5-10 mg/dose	Bradycardia, asystole, high-degree AV block, PR prolongation, hypotension, CHF	Use with β blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	
Adenosine	SVT	IV: 50-300 μg/kg by need rapid IV push Begin with 50 μg/kg and increase by 50-100 μg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, Atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, *N*-acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus–like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

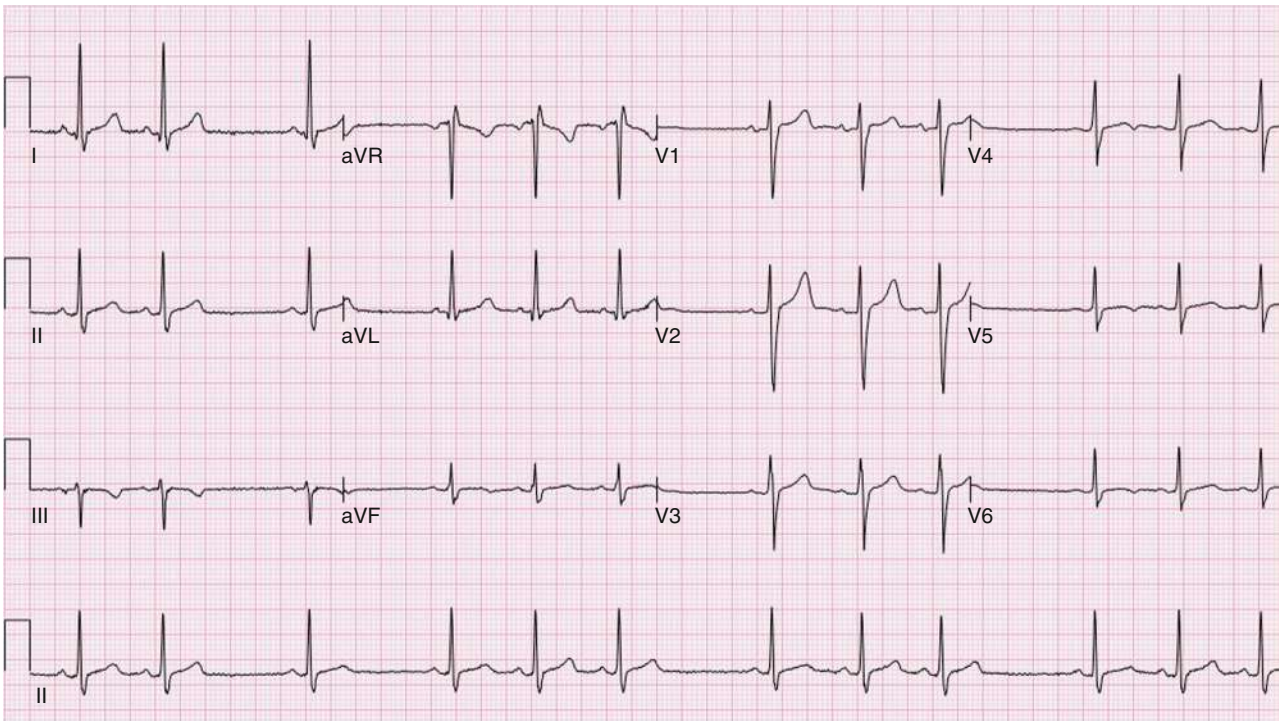

Fig. 484.1 Phasic sinus arrhythmia. Note the variation in P-P interval with no significant change in P-wave morphology or PR interval. This rhythm is normal.

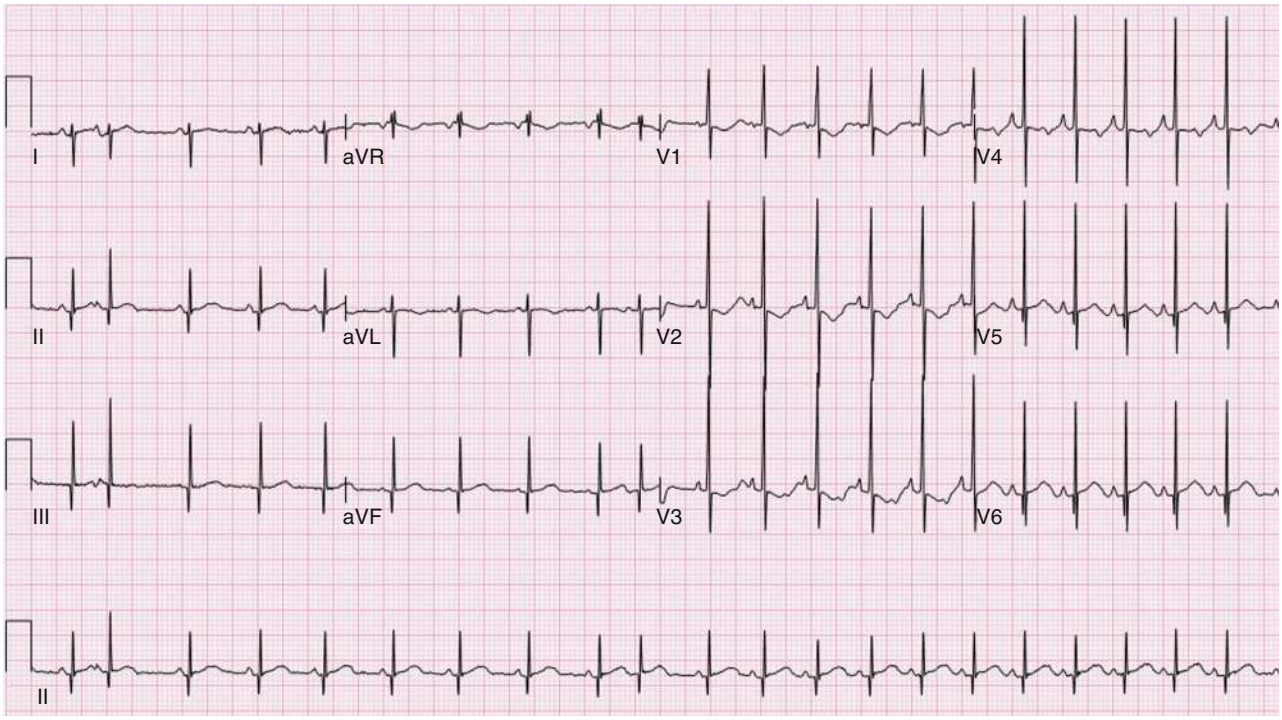

Fig. 484.2 Premature atrial contraction (PAC). The second and tenth beats are premature, and deformation of the previous T wave identifies the presence of a premature atrial contraction.

as *uniform or monomorphic,* suggesting origin from a common site. When PVCs vary in contour, they are designated as *multiform or polymorphic,* suggesting origin from more than one ventricular site. Ventricular extrasystoles are often, but not always, followed by a full compensatory pause because of a lack of resetting of the sinus node. The presence of **fusion beats**, that is, complexes with morphologic features that are intermediate between those of normal sinus beats and those of PVCs, proves the ventricular origin of the premature beat. Extrasystoles produce a smaller stroke and pulse volume than normal and, if quite premature, may not be audible with a stethoscope or palpable at the radial pulse. When frequent, extrasystoles may assume a definite rhythm, for example, alternating with normal beats **(bigeminy)** or occurring after two normal beats **(trigeminy)**. Most patients are unaware of single PVCs, although some may be aware of a "skipped beat" over the precordium. This sensation is caused by the increased stroke volume of the normal beat after a compensatory pause. Anxiety,

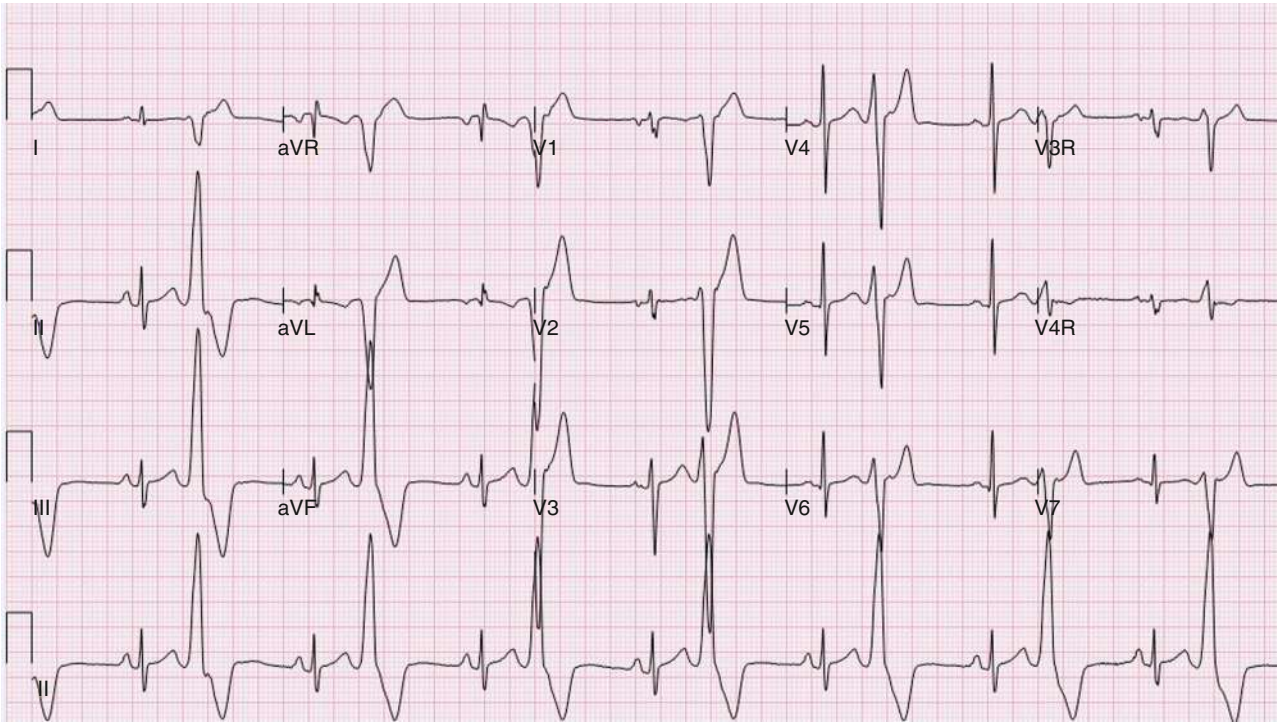

Fig. 484.3 Premature ventricular contractions in a bigeminal rhythm. Note that the premature beat is wide and has a completely different morphology from that of the sinus beat. The premature beat is not preceded by a discernible premature P wave or any appreciable deformation of the preceding T wave.

a febrile illness, or ingestion of various drugs or stimulants may make PVCs more frequent.

It is important to distinguish PVCs that are benign from those that are likely to lead to more severe arrhythmias. The former usually disappear (or are "suppressed) at higher sinus rates, as seen during exercise. If they persist or become more frequent during exercise, the arrhythmia may have greater significance. The following criteria are indications for further investigation of PVCs that could require **suppressive therapy**: (1) ≥2 PVCs in a row; (2) multiform PVCs; (3) increased ventricular ectopic activity with exercise; (4) R-on-T phenomenon (premature ventricular depolarization occurs on the T wave of the preceding beat); (5) extreme frequency of beats (e.g., >20% of total beats on Holter monitoring); and (6) most importantly, the presence of underlying heart disease, a history of heart surgery, or both. The best therapy for benign PVCs is reassurance that the arrhythmia is not life threatening, although highly symptomatic individuals may benefit from suppressive therapy.

Malignant PVCs are usually secondary to another medical problem (electrolyte imbalance, hypoxia, drug toxicity, cardiac injury, or a channelopathy). Successful treatment includes correction of the underlying abnormality if possible. An intravenous **lidocaine** bolus and drip is the first line of therapy, with more effective drugs such as **amiodarone** reserved for refractory cases or for patients with underlying ventricular dysfunction or hemodynamic compromise.

484.3 Supraventricular Tachycardia

Aarti S. Dalal and George F. Van Hare

Supraventricular tachycardia (SVT) is a general term that includes essentially all forms of paroxysmal or incessant tachycardia except ventricular tachycardia. The category of SVT can be divided into three major subcategories: reentrant tachycardias using an accessory pathway, reentrant tachycardias without an accessory pathway, and ectopic or automatic tachycardias. **Atrioventricular reciprocating tachycardia (AVRT)** involves an accessory pathway and is the most common mechanism of SVT in infants. **Atrioventricular node reentry tachycardia (AVNRT)** is rare in infancy but increases during childhood and into adolescence. **Atrial flutter** is rarely seen in children with normal hearts, whereas intraatrial reentry tachycardia (also known as *atrial flutter*) is sometimes seen in patients after cardiac surgery. Atrial and junctional ectopic tachycardias are more often associated with abnormal hearts (cardiomyopathy) and the immediate postoperative period after surgery for CHD.

CLINICAL MANIFESTATIONS

Reentrant SVT is characterized by an abrupt onset and termination; it may occur when the patient is at rest or exercising, and in infants it may be precipitated by an acute infection. Attacks may last only a few seconds or may persist for hours. The heart rate usually exceeds 180 beats/min in older children and adolescents and 220 bpm in infants and younger children. Rates of SVT are often as high as 300 beats/min in newborns and infants. The only complaint may be awareness of the rapid heart rate.

Many older children tolerate these episodes extremely well, and it is unlikely that short paroxysms are a danger to life. If heart rate is exceptionally rapid or the episode is prolonged, precordial discomfort and heart failure may occur. In children, SVT may be exacerbated by exposure to caffeine, nonprescription decongestants, or bronchodilators.

In young patients, the diagnosis may be more obscure because of their inability to communicate their symptoms. The heart rate during infancy is normally higher than in older children and increases greatly with crying. Occasionally, infants with SVT initially present with heart failure because the tachycardia may go unrecognized for a long time, **leading to tachycardia-induced cardiomyopathy**. The heart rate during SVT episodes is frequently in the range of 240-300 beats/min. If the episode lasts 6-24 hours or more, heart failure may be recognized, and the infant may present with poor feeding; an ashen color; and will be restless and irritable, with tachypnea, poor pulses, and hepatomegaly. When tachycardia occurs in the fetus, it can cause **hydrops fetalis**, the in utero manifestation of heart failure.

In neonates, SVT is usually manifested as a narrow QRS complex (<0.08 second). The P wave is visible on a standard ECG in only 50–60%

of neonates with SVT, but it is detectable with a transesophageal lead in most patients. *Differentiation from sinus tachycardia* may be difficult but is important because sinus tachycardia requires treatment of the underlying problem (e.g., sepsis, hypovolemia) rather than antiarrhythmic medication. If the rate is >230 beats/min with an abnormal P-wave axis (a normal P wave is positive in leads I and aVF), sinus tachycardia is *not* likely. The heart rate in SVT also tends to be *relatively fixed,* whereas in sinus tachycardia the heart rate *varies* with changes in parasympathetic and sympathetic tone. AVRT uses a bypass tract that may be able to conduct bidirectionally **(Wolff-Parkinson-White [WPW] syndrome)** or may be retrograde only **(concealed accessory pathway)**. Patients with WPW syndrome have a small but real risk of sudden death. If the accessory pathway rapidly conducts in antegrade fashion, the patient is at risk for atrial fibrillation begetting ventricular fibrillation. Risk stratification, including 24-hour Holter monitoring and exercise study, may help differentiate patients at higher risk for sudden death from WPW. However, it is important to note that intermittent preexcitation may not decrease a patient's risk profile. Syncope is an ominous symptom in WPW, and any patient with syncope and WPW syndrome should have an **electrophysiology study** (EPS) and consideration for catheter ablation.

The typical electrocardiographic features of WPW syndrome are seen when the patient is not having tachycardia. These features include a short P-R interval and slow upstroke of a widened QRS (delta wave) (Fig. 484.4). This may not be evident in every lead on an ECG. Although most often presenting in patients with a normal heart, WPW syndrome may also be associated with **Ebstein anomaly** of the tricuspid valve, congenitally corrected transposition of the great

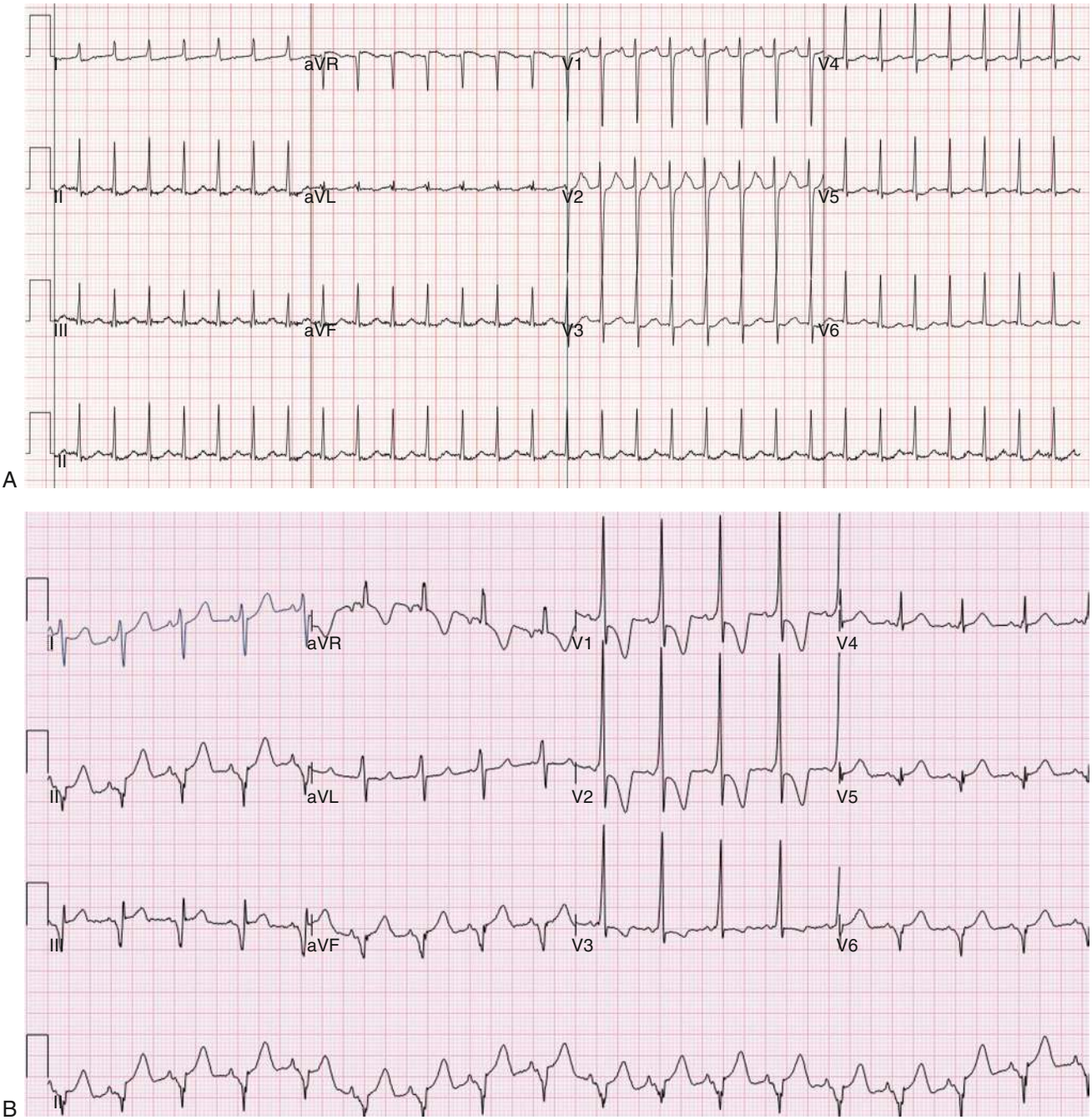

Fig. 484.4 A, Supraventricular tachycardia in a child with Wolff-Parkinson-White (WPW) syndrome. Note the normal QRS complexes during the tachycardia, as well as clear retrograde P waves seen on the upstroke of the T waves. B, Later, the typical features of WPW syndrome are apparent (short P-R interval, wide QRS with slurred upstroke known as a *delta wave*).

arteries, or certain forms of hypertrophic cardiomyopathy. WPW may also be associated with hypokalemic periodic paralysis, Danon disease, tuberous sclerosis, and rarely with pathogenic variants in *PRKAG2*.

The critical anatomic structure is an accessory pathway consisting of an electrically active myocardial fiber connecting atrium to ventricle on either the right or the left side of the AV ring (Fig. 484.5). During sinus rhythm, the impulse is carried over both the AV node and the accessory pathway; it produces some degree of fusion of the two depolarization fronts that results in an abnormal QRS complex. During AVRT, an impulse is carried in *antegrade* fashion through the AV node **(orthodromic tachycardia)**, which results in a normal QRS complex, and in *retrograde* fashion through the accessory pathway to the atrium, thereby perpetuating the tachycardia. In these cases, only after cessation of the tachycardia is the typical ECG features of WPW syndrome recognized (see Fig. 484.4). When rapid antegrade conduction occurs through the accessory pathway during tachycardia and the retrograde reentry pathway to the atrium is by the AV node **(antidromic tachycardia)**, the QRS complexes are wide and the potential for more serious arrhythmias (ventricular fibrillation) is greater, especially if atrial fibrillation occurs.

AVNRT involves the use of two functional pathways within the AV node: the *slow* and *fast* AV node pathways. This arrhythmia is more often seen in adolescence and young adulthood. It is one of the few forms of SVT that is occasionally associated with syncope. This arrhythmia is often seen in association with exercise.

TREATMENT

In infants, **vagal stimulation** can be induced by transiently placing an ice bag over the entire face to abort the attack for 15-30 seconds (this can be repeated if needed). Older children may be taught **vagal maneuvers** such as the Valsalva maneuver, straining, breath holding, or standing on their head. *Ocular pressure must never be performed, and carotid sinus massage is rarely effective*. When these measures fail, several pharmacologic alternatives are available (see Table 484.1). In stable patients, **adenosine** by rapid intravenous push is the treatment of choice (0.1 mg/kg, up to 6 mg) because of its rapid onset of action and minimal effects on cardiac contractility. The dose may need to be increased (0.2 mg/kg, up to 12 mg) if no effect on the tachycardia is seen. Because of the potential for adenosine to initiate atrial fibrillation, it should never be administered without a means for direct current **(DC) cardioversion** near at hand. Calcium channel blockers such as **verapamil** have also been used in the initial treatment of SVT in older children. Verapamil may reduce cardiac output and produce hypotension and cardiac arrest in infants younger than 1 year and therefore is contraindicated in this age-group. In urgent situations when symptoms of severe heart failure have already occurred, *synchronized* DC cardioversion (0.5-2 J/kg) is recommended as the initial management (see Chapter 79). Pace termination using esophageal pacing catheter is also an option.

Once the patient has been converted to sinus rhythm, a longer-acting agent is selected for maintenance therapy. In patients without an antegrade accessory pathway (non-WPW), the β-**adrenergic blockers** are the mainstay of drug therapy. **Digoxin** has been used for decades and may be effective in infants, but less so in older children. In children with WPW, digoxin or calcium channel blockers may *increase* the rate of antegrade conduction of impulses through the bypass tract, with the possibility of ventricular fibrillation, and are therefore contraindicated. These patients are usually managed with β blockers. In patients with resistant tachycardias, flecainide, propafenone, sotalol, and amiodarone are all acceptable next-line agents. Most antiarrhythmic agents have the potential of causing new dangerous arrhythmias (**proarrhythmia**) and decreasing heart function. Flecainide and propafenone should be limited to use in patients with hearts having otherwise normal cardiac function.

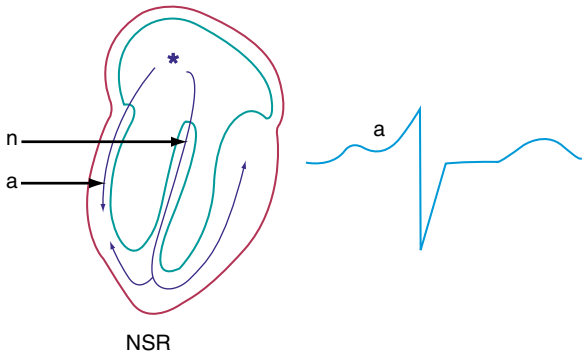

Fig. 484.5 Schematic representation of the heart with a right-sided accessory pathway (WPW syndrome). The *asterisk* indicates initiation of the sinus beat. The *arrows* indicate the direction and spread of excitation. The electrocardiographic complex shown represents a fusion beat that combines activation over the normal *(n)* and accessory *(a)* pathways. The latter inscribes the delta wave. NSR, Normal sinus rhythm.

If cardiac failure occurs because of prolonged tachycardia in an infant with a normal heart, cardiac function usually returns to normal after sinus rhythm is reinstituted, although it may take days to weeks. Infants with SVT diagnosed within the first 3-4 months of life have a lower incidence of recurrence than those initially diagnosed at a later age. These patients have up to an 80% chance of resolution by the first year of life, although approximately 30% will have recurrences later in childhood; if medical therapy is required, it can be tapered by 12-18 months and the patient watched for signs of recurrence. Parents should be taught to measure the heart rate in their infants, so that prolonged asymptomatic episodes of SVT may be detected before heart failure occurs.

The use of **24-hour electrocardiographic (Holter) monitoring** assists in following the course of therapy and detecting brief runs of asymptomatic tachycardia, particularly in younger children and infants. Direct-to-consumer heart monitoring devices ("wearables") are beginning to replace traditional monitors as newer technology allows for miniaturization and improved accuracy of at-home monitoring devices. These devices have helped identify asymptomatic tachycardia in infants and young children. Some centers use **transesophageal pacing** to evaluate the effects of therapy in infants. More detailed electrophysiology studies performed in the cardiac catheterization laboratory are often indicated in patients with refractory SVT who are candidates for catheter ablation. During an EPS, multiple electrode catheters are placed transvenously in different locations in the heart. Pacing is performed to evaluate the conduction characteristics of the accessory pathway and to initiate the tachyarrhythmia, and mapping is performed to locate the accessory pathway. **Catheter ablation** of an accessory pathway is frequently used in children and teenagers and in patients who require multiple agents or find drug side effects intolerable or for whom arrhythmia control is poor. Ablation may be performed either by **radiofrequency ablation**, which creates tissue heating, or **cryoablation**, in which tissue is frozen (Fig. 484.6). The overall initial success rate for catheter ablation in experienced pediatric laboratories ranges from 90% to 98%, depending on the location of the accessory pathway. Surgical ablation of bypass tracts is rarely done and proposed only in carefully selected patients.

The management of SVT caused by AVNRT is almost identical to that for AVRT. Children with AVNRT are not at increased risk of sudden death because they do not have a manifest accessory pathway. In practice, their episodes are more likely to be brought on by exercise or other forms of stress, and the heart rates can be quite fast, leading to chest pain, dizziness, and occasionally syncope. If chronic antiarrhythmic medication is desired, β blockers are the drugs of choice; acutely, AVNRT responds to adenosine. Less is known about the natural history, but patients with AVNRT are seen quite frequently in adulthood, so spontaneous resolution seems unlikely. Patients are quite amenable to catheter ablation, either using radiofrequency energy or cryoablation, with high success rates and low complication rates.

Atrial ectopic tachycardia is an uncommon tachycardia in childhood. It is characterized by a variable rate (seldom >200 beats/min), identifiable P waves with an abnormal axis, and either a sustained or incessant nonsustained tachycardia (Fig. 484.7). This form of atrial tachycardia has a single automatic focus. Identification of this mechanism is aided by monitoring the ECG while initiating vagal or pharmacologic therapy. Unlike reentrant tachycardias, which "break" suddenly, automatic tachycardias such as atrial tachycardia tend to

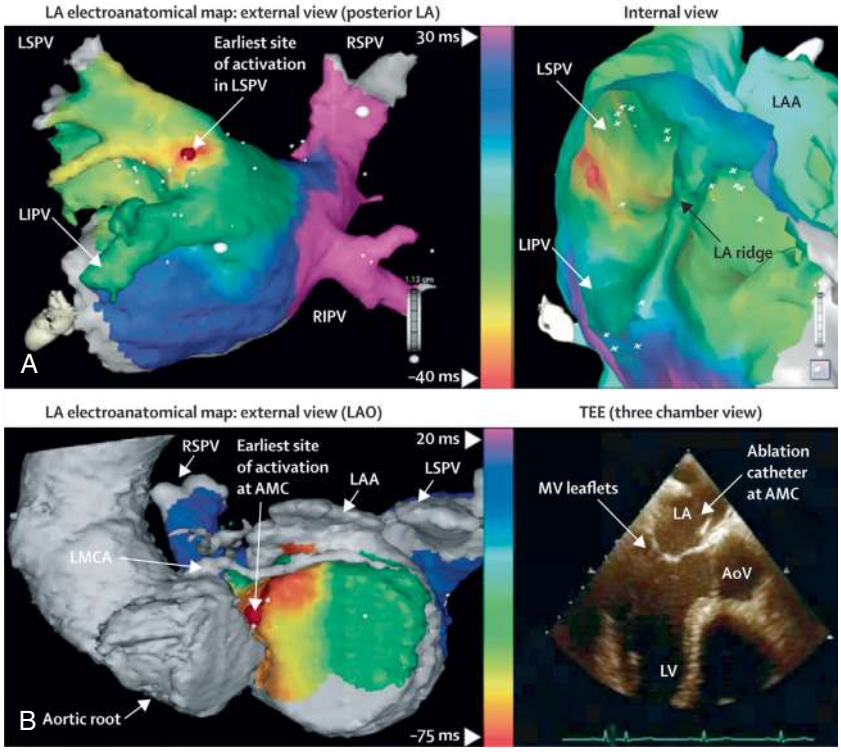

Fig. 484.6 Three-dimensional electroanatomic map of focal atrial tachycardias. Focal site of early activation *(red)* is shown, with radial propagation away from that central site. The activation map was superimposed onto the patient's cardiac CT scan, taken the day before the procedure and imported into the mapping system. This patient had two separate atrial foci. **A**, Tachycardia #1: Earliest site of activation, mapped to the posterior aspect of the LSPV ostium. Posterior external view *(left side)* and endoluminal or internal view looking posterior to anterior from within the left atrium into the mouth of the LSPV *(right side)* are shown. **B**, Tachycardia #2: Earliest site mapped to the aortomitral continuity. The anatomic relation between the mitral annulus and the aortic root can be clearly appreciated *(left side)*. The location of the ablation catheter at the site of earliest atrial activation during atrial tachycardia is shown on the TEE image *(right side)*. AMC, Aortomitral continuity; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary vein; LMCA, left main coronary artery; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; TEE, transesophageal echocardiogram. *(From Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: state of the art. Lancet. 2012;380:1509–1518, Fig 3.)*

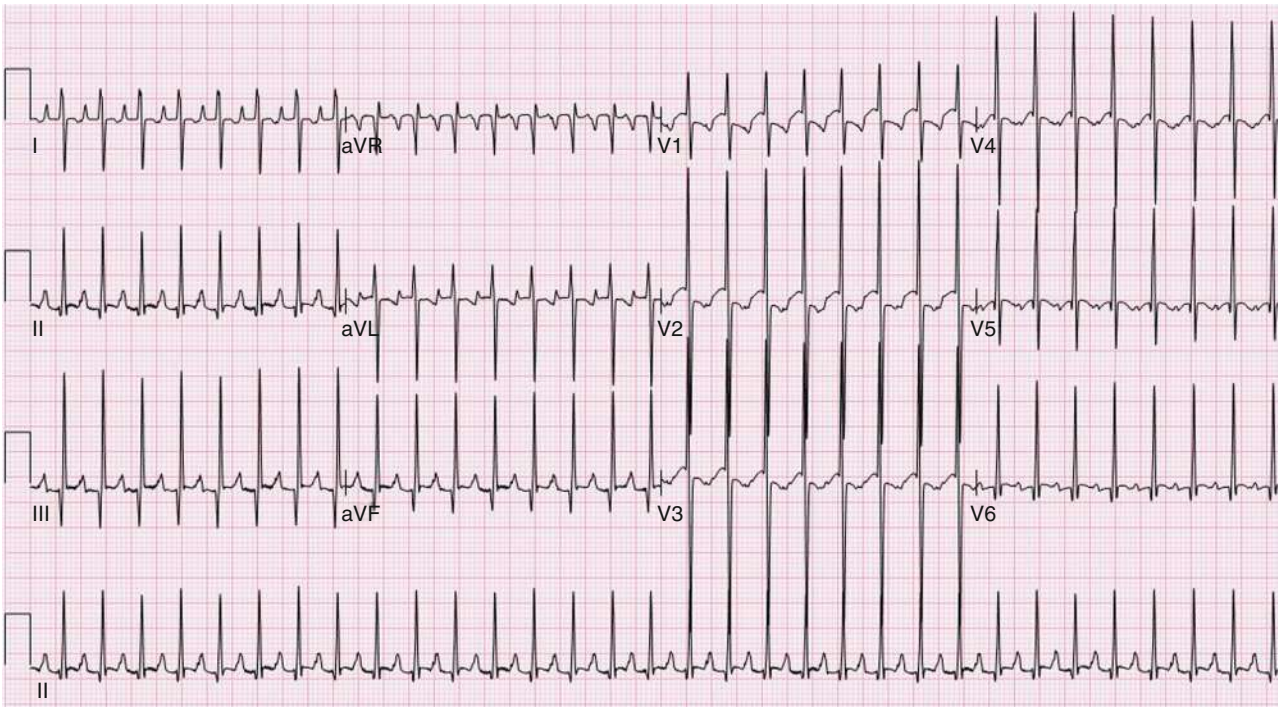

Fig. 484.7 Atrial ectopic tachycardia. Note the abnormal P waves and relative prolongation of the PR interval.

"warm up" and "cool down" (i.e., rates tend to gradually increase and decrease). Atrial ectopic tachycardias are usually more difficult to control pharmacologically than the more common reentrant tachycardias. If pharmacologic therapy with a single agent is unsuccessful, catheter ablation is suggested and has a high success rate, usually >90%. Long-term treatment or ablation may not be necessary in some cases, as atrial ectopic tachycardia may resolve spontaneously in some patients.

Chaotic or multifocal atrial tachycardia is defined as atrial tachycardia with ≥3 ectopic P-wave morphologies, frequent blocked P waves, and varying P-R intervals of conducted beats. This arrhythmia occurs most often in infants younger than 1 year of age, usually without concomitant cardiac disease, although some evidence suggests an association with viral myocarditis or pulmonary disease. The goal of drug treatment is rate control, or slowing of the ventricular rate, because conversion to sinus rhythm may not be possible. Multiple agents are often required. When this arrhythmia occurs in infancy, it usually terminates spontaneously by 3 years of age.

Accelerated junctional ectopic tachycardia (JET) is an automatic (non-reentry) arrhythmia in which the junctional rate exceeds that of the sinus node and AV dissociation may result. This arrhythmia is most often recognized in the early postoperative period after cardiac surgery and may be extremely difficult to control. Reduction of the infusion rate of exogenous catecholamines and mitigating causes of endogenous catecholamines such as fever and pain are important adjuncts to management. Intravenous amiodarone and procainamide are effective in the treatment of postoperative JET. Congenital JET may be seen in the absence of surgery. It is often incessant, can be difficult to treat, and can lead to a dilated cardiomyopathy. Patients who require chronic therapy may respond to amiodarone or sotalol. Congenital JET can be cured by catheter ablation, but long-term AV block requiring a pacemaker is an occasional important complication.

Atrial flutter, also known as *intraatrial reentrant tachycardia,* is an atrial tachycardia characterized by atrial activity at a rate of 250-300 beats/min in children and adolescents and 400-600 beats/min in neonates. The mechanism of common atrial flutter consists of a reentrant rhythm originating in the right atrium circling the tricuspid valve annulus. Because the AV node cannot transmit such rapid impulses, some degree of **AV block** is virtually always present, and the ventricles respond to every second to fourth atrial beat (Fig. 484.8). Occasionally, the response is variable, and the rhythm appears irregular.

In older children, atrial flutter usually occurs in the setting of CHD; neonates with atrial flutter frequently have normal hearts. Atrial flutter may occur during acute infectious illnesses but is most often seen in patients with large stretched atria, such as those associated with long-standing mitral or tricuspid insufficiency, tricuspid atresia, Ebstein anomaly, or rheumatic mitral stenosis. Atrial flutter can also occur after any palliative or corrective cardiac surgery involving an atriotomy. Uncontrolled atrial flutter may precipitate heart failure. Vagal maneuvers or adenosine may produce a temporary slowing of the heart rate as a result of increased AV block, allowing a diagnosis to be made. The diagnosis is confirmed by ECG, which demonstrates the rapid and regular atrial saw-toothed flutter waves. *Atrial flutter usually converts immediately to sinus rhythm by synchronized DC cardioversion, which is most often the treatment of choice.* If pacing wires or atrial pacemaker leads are present, pace termination with atrial overdriving pacing may be a treatment option. In infants, an esophageal pacing lead can also be used, but care must be taken to avoid inadvertent ventricular pacing. Patients with chronic atrial flutter in the setting of CHD may be at increased risk for thromboembolism and stroke and should thus undergo anticoagulation before elective cardioversion. β Blockers or calcium channel blockers may be used to slow the ventricular response in atrial flutter by prolonging the AV node refractory period. Other agents may be used to maintain sinus rhythm, including **class I agents** such as procainamide or propafenone or **class III** agents such as amiodarone and sotalol. **Catheter ablation** has been used in patients with normal hearts and those with CHD with moderate success. After cardioversion, neonates with normal hearts may be followed off antiarrhythmic therapy or may be treated with digoxin, propranolol, or sotalol for 6-12 months, after which the medication can usually be discontinued, because neonatal atrial flutter generally does not recur.

Atrial fibrillation is uncommon in children and is rare in infants. The atrial excitation is chaotic and more rapid (400-700 beats/min) and produces an *irregularly irregular* ventricular response and pulse (Fig. 484.9). This rhythm disorder is often associated with atrial

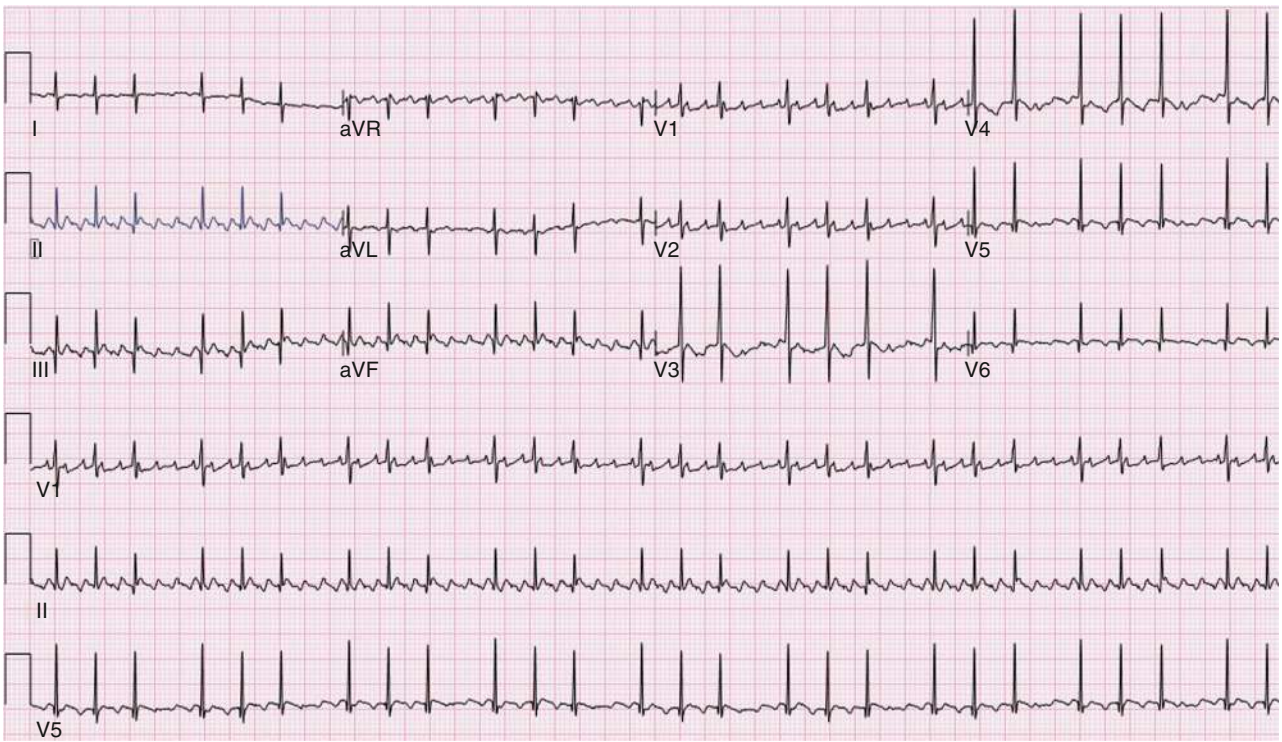

Fig. 484.8 Neonatal atrial flutter. Note that there is variable AV conduction and the flutter waves have a cycle length of 160 msec, corresponding to an atrial rate of 375 bpm.

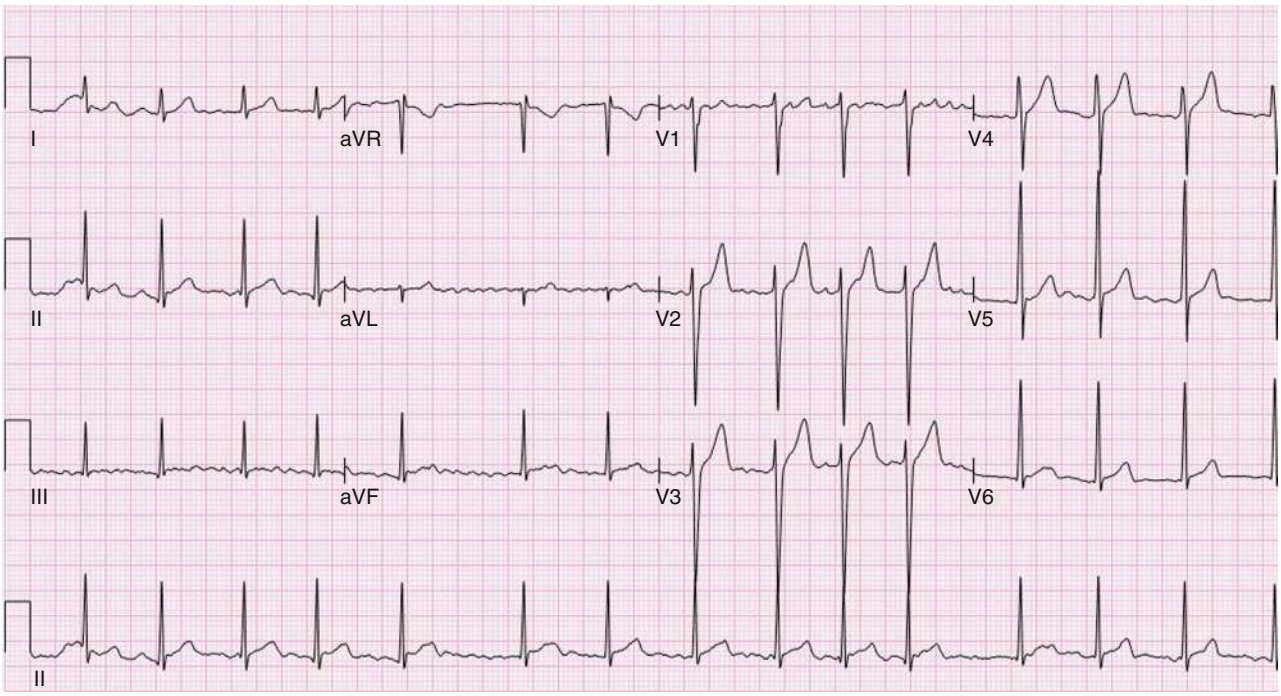

Fig. 484.9 Atrial fibrillation, characterized by the absence of clear P waves and an irregularly irregular ventricular response. One can appreciate the irregular, rapid undulations (F waves). Fibrillatory waves may not be visible in all leads and should be carefully sought in every tracing with irregular R-R intervals. Note that no two R-R intervals are the same.

enlargement or disease. Atrial fibrillation may be seen in older children with rheumatic mitral valve stenosis. It is also seen rarely as a complication of atrial surgery, in patients with left atrial enlargement secondary to left AV valve insufficiency, and in patients with WPW syndrome. Thyrotoxicosis, pulmonary embolism, pericarditis, or cardiomyopathy may be suspected in a previously normal older child or adolescent who presents with atrial fibrillation. Very rarely, atrial fibrillation may be familial and is usually an autosomal dominant disorder often affecting the potassium or sodium channel genes. The best initial treatment is **rate control**, most effectively with calcium channel blockers, to limit the ventricular rate during atrial fibrillation. Digoxin is not given if WPW syndrome is present. Normal sinus rhythm may be restored with intravenous procainamide, ibutilide, or amiodarone; DC cardioversion is the first choice in hemodynamically unstable patients. Patients with chronic atrial fibrillation are at risk for thromboembolism and stroke and should undergo anticoagulation with warfarin. Patients being treated by elective cardioversion should also undergo anticoagulation.

484.4 Ventricular Tachyarrhythmias

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Ventricular tachycardia (VT) is much less common than SVT in pediatric patients. VT is defined as at least three PVCs at >120 beats/min (Fig. 484.10). It may be paroxysmal or incessant. VT can be seen in congenital or acquired heart disease, including inherited arrhythmia syndromes secondary to channelopathies, myopathies, or laminopathies. VT may be associated with structural disease such as myocarditis, anomalous origin of a coronary artery, mitral valve prolapse, primary cardiac tumors, arrhythmogenic cardiomyopathy (previously known as *arrhythmogenic right ventricular cardiomyopathy*), dilated or hypertrophic cardiomyopathy, and cardiac laminopathies (associated with lamin A/C gene pathogenic variants). Patients with laminopathies associated with a variant in the lamin A/C gene *(LMNA)*, as seen in Emery Dreifuss muscular dystrophy or 1B limb girdle muscular dystrophy are at risk of primary ventricular arrhythmias in addition to development of cardiomyopathies. VT can also be seen in patients with channelopathies such as catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, *TANGO2*-related encephalopathy and arrhythmias, and long QT syndrome. A prolonged QT interval of either congenital or acquired (proarrhythmic medication or hypokalemia, hypocalcemia, hypomagnesemia) causation can increase a patient's risk of arrhythmias. Other causes include WPW syndrome and drug use (cocaine, amphetamines). VT may develop years after intraventricular surgery (especially tetralogy of Fallot and related defects) or occur without obvious organic heart disease. VT must be distinguished from SVT with aberrancy or rapid conduction over an accessory pathway (Table 484.2). The presence of clear capture and fusion beats confirms the diagnosis of VT. Although some children tolerate rapid ventricular rates for many hours, this arrhythmia should be promptly treated because hypotension and degeneration into ventricular fibrillation may result. For patients who are hemodynamically stable, intravenous amiodarone, lidocaine, and procainamide are the initial drugs of choice. If treatment is to be successful, it is critical to search for and correct any underlying abnormalities, such as electrolyte imbalance, hypoxia, or drug toxicity. **Amiodarone** is the treatment of choice during cardiac arrest (see Chapter 79). Hemodynamically unstable patients with VT should be immediately treated with DC cardioversion. Overdrive ventricular pacing, through temporary pacing wires or a permanent pacemaker, may also be effective, although it may cause the arrhythmia to deteriorate into ventricular fibrillation. In the neonatal period, VT may be associated with an anomalous left coronary artery (see Chapter 481.2) or a myocardial tumor.

Unless a clearly reversible cause is identified, an electrophysiology study is usually indicated for patients in whom VT has developed, and depending on the findings, catheter ablation and/or implantable cardioverter-defibrillator (ICD) implantation may be indicated.

A related arrhythmia, **ventricular accelerated rhythm**, is occasionally seen in infants. It is defined the same way as VT, but the rate is only slightly faster than the coexisting sinus rate (within 10%). It is generally benign and resolves spontaneously.

Ventricular fibrillation (VF) is a chaotic rhythm that results in death unless an effective ventricular beat is rapidly reestablished. Usually, cardiopulmonary resuscitation and DC defibrillation are necessary. If defibrillation is ineffective or VF recurs, amiodarone or lidocaine may be given intravenously and defibrillation repeated (see Chapter 79). After recovery from VF, a search should be made for the

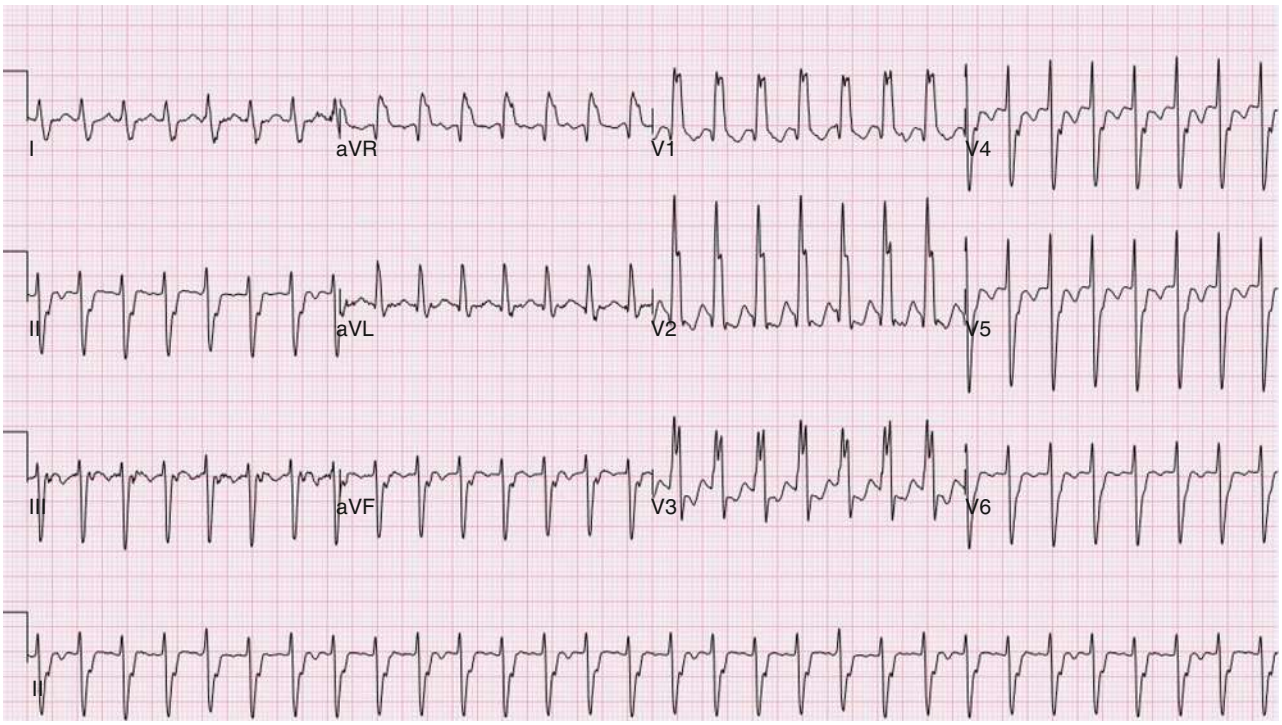

Fig. 484.10 Ventricular tachycardia. The QRS complexes are wide and abnormal. Atrioventricular dissociation can be best appreciated in the lead II rhythm strip at the bottom.

Table 484.2 Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P-wave morphology and axis	Normal or prolonged (with aberration)	Usually regular, but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no two R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Saw-tooth flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2:1, 3:1, 3:2)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

underlying cause. EPS is indicated for patients who have survived VF unless a clearly reversible cause is identified. If WPW syndrome is noted, catheter ablation should be performed. For patients in whom no correctable abnormality can be found, an ICD is almost always indicated because of the high risk of sudden death.

484.5 Long QT Syndromes

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Long QT syndrome is a genetic abnormality of ventricular repolarization, with an estimated incidence of about 1 per 10,000 births (Table 484.3; also includes other genetic arrhythmia syndromes). It presents as a long QT interval on the surface ECG and is associated with malignant ventricular arrhythmias (**torsades de pointes** and VF). Long QT syndrome can cause syncope and sudden death and may be the cause of some cases of sudden infant death syndrome, drowning, and intrauterine fetal demise (Fig. 484.11). In perhaps 80% of cases, there is an identifiable pathogenic variant. The distinction between dominant and recessive forms of the disease (Romano-Ward syndrome vs Jervell-Lange-Nielsen syndrome) is no longer made because the latter recessive condition is known to result from the homozygous state. **Jervell-Lange-Nielsen syndrome** is associated with congenital sensorineural deafness. Asymptomatic but at-risk patients carrying the gene variant may not all have a prolonged QT duration. QT interval prolongation may become apparent with exercise, position change or during catecholamine infusions.

Genetic studies have identified pathogenic variants in cardiac potassium and sodium channels (see Table 484.3). Additional forms (up to 13 variants) of long QT syndrome (LQTS) have been described, but these are much less common. Genotype may predict clinical manifestations;

LQTS type 1 (**LQT1**) events are usually induced by stress or exertion, whereas events in **LQT3** often occur at rest, especially during sleep (see Fig. 484.11). **LQT2** events have an intermediate pattern, often occurring in the postpartum period or with auditory triggers. LQT3 has the highest probability for sudden death, followed by LQT2 and then LQT1. Drugs may prolong the QT interval directly but more often do so when drugs such as erythromycin or ketoconazole inhibit their metabolism (Table 484.4).

The **clinical manifestation** of LQTS in children is most often a syncopal episode brought on by exercise, fright, or a sudden startle; some events occur during sleep (LQT3). Patients can initially be seen with seizures, presyncope, or palpitations; approximately 10% are initially in cardiac arrest. The diagnosis is based on electrocardiographic and clinical criteria. Not all patients with long QT intervals have LQTS, and patients with normal QT intervals on a resting ECG may have LQTS. A heart rate–corrected QT interval (QTc) of >0.47 second is highly indicative, whereas a QTc interval of >0.44 second is suggestive. Other features include notched T waves in three leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or unexplained sudden death. Exercise testing, provocative drug testing, and 24-hour Holter monitoring are adjuncts to the diagnosis. Genotyping is available and can identify the pathogenic variant in approximately 80% of patients known to have LQTS by clinical criteria. Genotyping is not useful in ruling out the diagnosis in individuals with suspected disease, but when positive is very useful in identifying asymptomatic affected relatives of the index case.

Short QT syndromes manifest with atrial or ventricular fibrillation and are associated with syncope and sudden death (see Table 484.3). They are often caused by a gain-of-function mutation in cardiac potassium channels.

Treatment of LQTS includes the use of β-blocking agents at doses that blunt sympathetic tone. Nonselective β blockers such as propranolol and nadolol seem to be more effective than atenolol and metoprolol for some genotypes. Some patients require a **pacemaker** because of drug-induced bradycardia. An **implantable cardiac defibrillator** (ICD) is indicated in patients with continued syncope despite treatment with β blockers and those who have experienced cardiac arrest. Genotype-phenotype correlative studies suggest that β blockers are not as effective in patients with LQT3, but these patients may respond to mexiletine with shortening of the QT interval.

484.6 Sinus Node Dysfunction

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Sinus arrest and sinoatrial block may cause a sudden pause in the heartbeat. **Sinus arrest** is presumably caused by failure of impulse formation within the sinus node. **Sinoatrial block** results from a block between the sinus pacemaker complex and the surrounding atrium. These arrhythmias are rare in childhood except in patients who have had extensive atrial surgery.

Sick sinus syndrome is the result of abnormalities in the sinus node or atrial conduction pathways, or both. This syndrome may occur in the absence of CHD and has been reported in siblings, but it is most commonly seen after surgical correction of congenital heart defects,

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes

GENE	LOCUS	PROTEIN
LONG QT SYNDROME (LQTS)		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (Na_v1.5)
Minor LQTS Genes (Listed Alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21	Calmodulin 2
CALM3	19q13.2-q13.3	Calmodulin 3
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel $beta_4$ subunit
SNTA1	20q11.2	Syntrophin-$alpha_1$
TRIADIN KNOCKOUT (TKO) SYNDROME		
TRDN	6q22.31	Cardiac triadin
ANDERSEN-TAWIL SYNDROME (ATS)		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
TIMOTHY SYNDROME (TS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
Cardiac-Only TS (COTS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v1.2)
SHORT QT SYNDROME (SQTS)		
KCNH2 (SQT1)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v11.1)
KCNQ1 (SQT2)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v7.1)

Continued

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes—cont'd

GENE	LOCUS	PROTEIN
KCNJ2 (SQT3)	17q23	I_{K1} potassium channel (Kir2.1)
CACNA1C (SQT4)	12p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNB2 (SQT5)	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
CACN2D1 (SQT6)	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)
CALM1	14q32.11	Calmodulin 1
CALM3	19q13.2-q13.3	Calmodulin 3
TRDN	6q22.31	Cardiac triadin
BRUGADA SYNDROME (BRS)		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
Minor Brs Genes (Listed Alphabetically)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
FGF12	3q28	Fibroblast growth factor 12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1–like
KCND3	1p13.2	Voltage-gated potassium channel (I_{to}) subunit $K_v4.3$
KCNE3	11q13.4	Potassium channel $beta_3$ subunit (MiRP2)
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
HEY2	6q	Hes-related family BHLH transcription factor with YRPW motif 2
PKP2	12p11	Plakophilin-2
RANGRF	17p13.1	RAN guanine nucleotide release factor 1
SCN1B	19q13	Sodium channel $beta_1$
SCN2B	11q23	Sodium channel $beta_2$
SCN3B	11q24.1	Sodium channel $beta_3$
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
SLMAP	3p14.3	Sarcolemma-associated protein
EARLY REPOLARIZATION SYNDROME (ERS)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel ($Ca_v1.2$)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit ($Na_v1.8$)
IDIOPATHIC VENTRICULAR FIBRILLATION (IVF)		
ANK2	4q25-q27	Ankyrin B
CALM1	14q32.11	Calmodulin 1
DPP6	7q36	Dipeptidyl-peptidase-6
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
RYR2	1q42.1-q43	Ryanodine receptor 2
SCN3B	11q23	Sodium channel $beta_3$ subunit

Table 484.3 Heritable Arrhythmia Syndrome Susceptibility Genes—cont'd

GENE	LOCUS	PROTEIN
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
PROGRESSIVE CARDIAC CONDUCTION DISEASE/DEFECT (PCCD)		
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
TRPM4	19q13.33	Transient receptor potential cation channel, subfamily M, member 4
SICK SINUS SYNDROME (SSS)		
ANK2	4q25-q27	Ankyrin B
HCN4	15q24-q25	Hyperpolarization-activated cyclic nucleotide–gated channel 4
MYH6	14q11.2	Myosin, heavy chain 6, cardiac muscle, alpha
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)
"ANKYRIN-B SYNDROME"		
ANK2	4q25-q27	Ankyrin B
FAMILIAL ATRIAL FIBRILLATION (FAF)		
ANK2	4q25-q27	Ankyrin B
GATA4	8p23.1-p22	GATA-binding protein 4
GATA5	20q13.33	GATA-binding protein 5
GJA5	1q21	Connexin 40
KCNA5	12p13	I_{Kur} potassium channel ($K_v1.5$)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNH2	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, $K_v11.1$)
KCNJ2	17q23	I_{K1} potassium channel (Kir2.1)
KCNQ1	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, $K_v7.1$)
NPPA	1p36	Atrial natriuretic peptide precursor A
NUP155	5p13	Nucleoporin 155 kD
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit ($Na_v1.5$)

From Tester DJ, Ackerman MJ. Genetics of cardiac arrhythmias. In Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier; 2019, Table 33.1, p. 605.

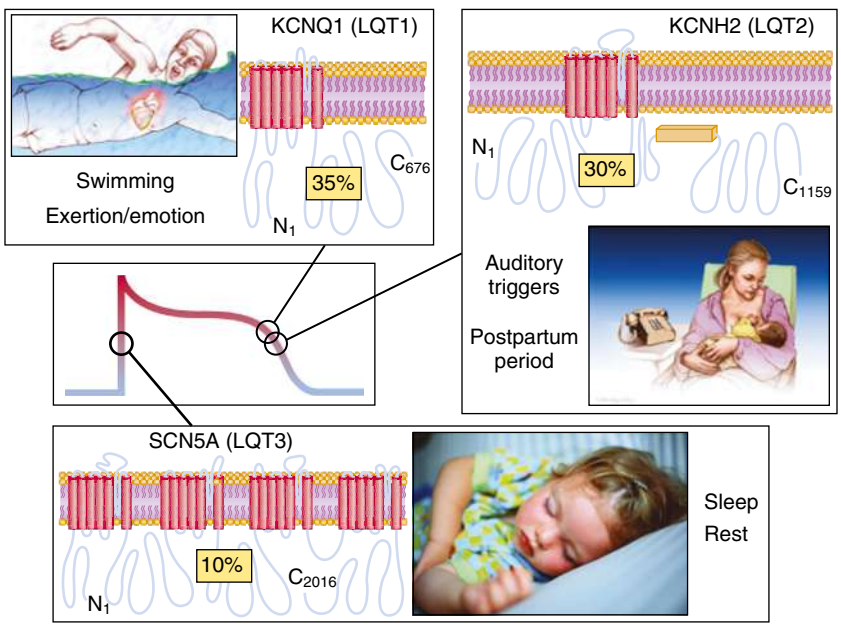

Fig. 484.11 Genotype-phenotype correlations in long QT syndrome (LQTS). About 75% of clinically strong LQTS is caused by mutations in three genes (35% *KCNQ1*, 30% *KCNH2*, and 10% *SCN5A*) encoding for ion channels that are critically responsible for the orchestration of the cardiac action potential. Observed genotype-phenotype correlations include swimming/exertion/emotion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3. *(From Tester DJ, Ackerman MJ. Genetics of cardiac arrhythmias. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig 33-3, p. 607.)*

Table 484.4 Acquired Causes of QT Prolongation*

DRUGS
Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones†
Antifungal agents†—fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, *N*-acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K^+ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—ondansetron, HIV protease inhibitors, Chinese herbs
ELECTROLYTE DISTURBANCES
Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia
UNDERLYING MEDICAL CONDITIONS
Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

*A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.crediblemeds.org).
†Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.
From Park MY. *Pediatric Cardiology for Practitioners,* 5th ed. Philadelphia: Mosby; 2008: Box 24-1, p. 433.

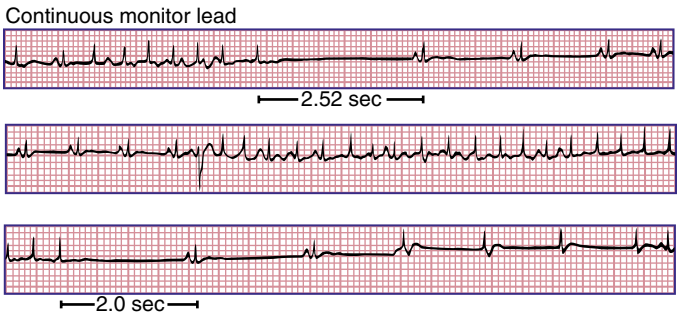

Fig. 484.12 The "tachy-brady" syndrome with sinus node dysfunction. Note the bursts of supraventricular tachycardia, probably multifocal atrial in origin, followed by long periods of sinus arrest and by sinus bradycardia. Often, symptoms are caused by the long sinus pauses after termination of tachycardia, rather than by the tachycardia itself.

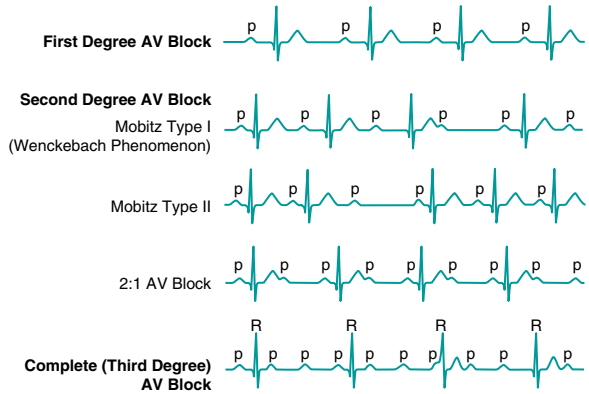

Fig. 484.13 Atrioventricular (AV) block. *(From Park MY. Pediatric Cardiology for Practitioners, 5th ed. Philadelphia: Mosby; 2008: Fig 25-1, p. 446.)*

especially the **Fontan procedure** and the **atrial switch** (Mustard or Senning) operation for transposition of the great arteries. Clinical manifestations depend on the heart rate. Most patients remain asymptomatic without treatment, but dizziness and syncope can occur during periods of marked sinus slowing with failure of junctional escape. Pacemaker therapy is indicated in patients who experience symptoms such as exercise intolerance or syncope.

Patients with sinus node dysfunction may also have episodes of SVT **("tachy-brady" syndrome)** with symptoms of palpitations, exercise intolerance, or dizziness (Fig. 484.12). Treatment must be individualized. Drug therapy to control tachyarrhythmias (propranolol, sotalol, amiodarone) may suppress sinus and AV node function to such a degree that further symptomatic bradycardia may be produced. Therefore insertion of a pacemaker in conjunction with drug therapy is usually necessary for such patients, even in the absence of symptoms ascribable to low heart rate.

484.7 Atrioventricular Block

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Atrioventricular block may be divided into three forms (Fig. 484.13). In **first-degree AV block**, the PR interval is prolonged but all the atrial impulses are conducted to the ventricle. In **second-degree AV block**, not every atrial impulse is conducted to the ventricle. In the variant of second-degree block known as the **Wenckebach type** (also called **Mobitz type I**), the PR interval increases progressively until a P wave is not conducted. In the cycle following the dropped beat, the PR interval normalizes. In **Mobitz type II** there is no progressive conduction delay or subsequent shortening of the PR interval after a blocked beat. This conduction defect is less common but has more potential to cause syncope and may be progressive. A related condition is **high-grade second-degree AV block**, in which two or more P waves in a row fail to conduct. This is even more dangerous. In **third-degree AV block (complete heart block)**, no impulses from the atria reach the ventricles. An independent escape rhythm is usually present but may not be reliable, leading to syncope or even sudden death.

Congenital complete AV block in children is presumed to be caused by autoimmune injury of the fetal conduction system by maternally derived immunoglobulin G antibodies (anti-SSA/Ro, anti-SSB/La) in a mother with overt or, more often, asymptomatic systemic lupus erythematosus (SLE) or Sjögren syndrome. Autoimmune disease accounts for 60–70% of all cases of congenital complete AV block and 80% of cases in which the heart is structurally normal (Fig. 484.14). A pathogenic variant in *NKX2-5* is associated with congenital AV block and an atrial septal defect.

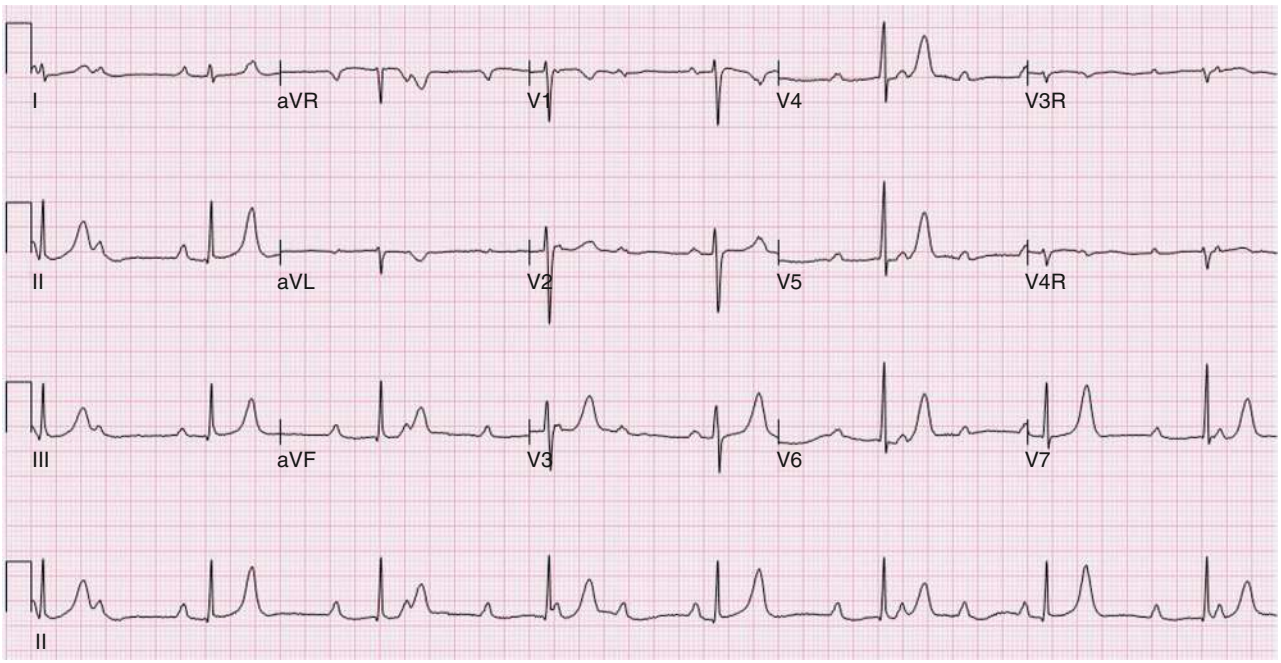

Fig. 484.14 Congenital complete atrioventricular (AV) block. The ventricular rate is regular at 44 beats/min. The atrial rate is approximately 100 beats/min and completely dissociated from the ventricle. The QRS morphology is normal, which is common in congenital complete AV block.

Complete AV block is also seen in patients with complex CHD and abnormal embryonic development of the conduction system. It has been associated with myocardial tumors and myocarditis. Acquired heart block (first, second, or third degree) is seen in Lyme disease and COVID-19–associated multisystem inflammatory syndrome. In these syndromes, first-degree heart block may progress to second- or third-degree heart block. Complete AV block is a known complication of myocardial abscess secondary to endocarditis. It is also seen in genetic conditions, including LQTS, Emery Dreifuss muscular dystrophy, and Kearns-Sayre syndrome. Postoperative AV block can be a complication of CHD repair—in particular, those repairs involving closure of a ventricular septal defect.

The incidence of congenital complete AV block is 1 per 20,000-25,000 live births; a high fetal loss rate may cause an underestimation of its true incidence. In some infants of mothers with SLE, complete AV block is not present at birth but develops within the first 3-6 months after birth. The arrhythmia is often diagnosed in the fetus (secondary to the dissociation between atrial and ventricular contractions seen on fetal echocardiography) and may produce hydrops fetalis. Maternal treatment with corticosteroids to halt progression or reverse AV block is controversial. Infants with associated CHD and heart failure have a high mortality rate.

In older children with otherwise normal hearts, complete AV block is often asymptomatic, although syncope and sudden death may occur. Infants and toddlers may have night terrors, tiredness with frequent naps, and irritability. The peripheral pulse is prominent because of the compensatory large ventricular stroke volume and peripheral vasodilation; systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve (cannon wave). Exercise and atropine may produce an acceleration of 10-20 beats/min. Systolic murmurs are frequently audible along the left sternal border, and apical mid-diastolic murmurs are not unusual. The first heart sound is variable because of variable ventricular filing with AV dissociation. AV block may result in enlargement of the heart because of slow rates and increased diastolic ventricular filling.

The **diagnosis** is confirmed by electrocardiography; the P waves and QRS complexes have no constant relationship (see Fig. 484.14). The QRS duration may be prolonged, or it may be normal if the heartbeat is initiated high in the AV node or bundle of His.

The **prognosis** for congenital complete AV block is usually favorable; patients who have been observed to age 30-40 have lived normal, active lives. Some patients have episodes of exercise intolerance, dizziness, and syncope (Stokes-Adams attacks); syncope requires the implantation of a permanent cardiac pacemaker. Pacemaker implantation should be considered for patients who develop symptoms such as progressive cardiac dilation, prolonged pauses, or daytime average heart rates of ≤50 beats/min. In addition, prophylactic pacemaker implantation in adolescents is reasonable considering the low risk of the implant procedure and the difficulty in predicting who will develop sudden severe symptoms.

Cardiac pacing is recommended in neonates with low ventricular rates (≤55 beats/min), evidence of heart failure, wide complex rhythms, or CHD (with ventricular rates <70 beats/min). Isoproterenol, atropine, or epinephrine may be tried to increase the heart rate temporarily until pacemaker placement can be arranged. Transthoracic epicardial pacemaker implants have traditionally been used in infants; transvenous placement of pacemaker leads is available for young children. Postsurgical complete AV block can occur after any open heart procedure requiring suturing near the AV valves or crest of the ventricular septum. Postoperative heart block is initially managed with temporary pacing wires. The likelihood of a return of normal conduction after 10-14 days is low; a permanent pacemaker is recommended after that time.

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Chapter 485

Sudden Death

Aarti S. Dalal and George F. Van Hare

Sudden death other than sudden infant death syndrome is rare in children. The causes of sudden death can be divided into traumatic versus nontraumatic in origin. *Traumatic* causes of sudden death are the most common in children; these include motor vehicle crashes, violent deaths, recreational deaths, and occupational deaths. *Nontraumatic* sudden deaths are often the result of specific cardiac causes. The incidence of sudden death varies from 0.8 to 6.2 per 100,000 per year in children and adolescents, in contrast to the higher incidence of **sudden cardiac death (SCD)** in adults of 1 per 1,000. Approximately 65% of sudden deaths are a result of heart-related problems in patients with either normal or congenitally (repaired, palliated, or unoperated) abnormal hearts. Competitive high school **sports** (basketball, soccer, football) are high-risk environmental factors. Common identifiable causes of death in competitive athletes include hypertrophic cardiomyopathy, with or without obstruction to left ventricular outflow, other cardiomyopathies, channelopathies, and anomalous coronary arteries; most are sudden *unexplained* deaths (Fig. 485.1). Table 485.1 lists other potential causes. These can be classified as *structural* abnormalities, including aortic stenosis and coronary artery abnormalities; myocardial disease, such as myocarditis; conduction system disease, including long QT syndrome; and miscellaneous causes, including seizures, pulmonary hypertension, and commotio cordis. Symptoms may be absent before the event but, if present, include syncope, chest pain, dyspnea, exercise intolerance, and palpitations. Patients may have a family history of heart disease (dilated or hypertrophic cardiomyopathy, long QT interval, arrhythmogenic [right ventricular] cardiomyopathy, Brugada or Marfan syndromes) or sudden unexplained death. Death often follows exertion or exercise. Some patients with sudden death during sports have anatomically normal hearts at autopsy; these patients should undergo genetic testing for hereditary arrhythmia syndromes.

MECHANISM OF SUDDEN DEATH

There are three recognized mechanisms of sudden death: *arrhythmic, nonarrhythmic cardiac* (circulatory and vascular causes), and *noncardiac*. **Ventricular fibrillation (VF)**, although the most common final cause of sudden death in adults, is only the final cause in 10–20% of children with SCD. More often, **bradycardia** leads either to VF or asystole (see Chapter 484).

CONGENITAL HEART DISEASE

Valvar aortic stenosis is the congenital defect most often associated with sudden death in children. Historically, approximately 5% of children with this disease die, although this has become quite rare in the modern era. A history of syncope, chest pain, and evidence of severe obstruction and left ventricular hypertrophy are risk factors (see Chapter 476.5).

Coronary artery anomalies are also frequently associated with sudden death in children and adolescents. The most common abnormality associated with sudden death is the origin of the left main coronary artery from the right sinus of Valsalva. The coronary artery takes an interarterial course between the aorta and pulmonary artery and may also have an intramural course, traveling within the ventricular myocardium. Exercise results in a rise in pulmonary and aortic pressure, and this is thought to compress the left main coronary artery and results in ischemia caused by compression or kinking. Anomalous origin of the right coronary artery from the left sinus of Valsalva is much more common, but only rarely is a cause of sudden death.

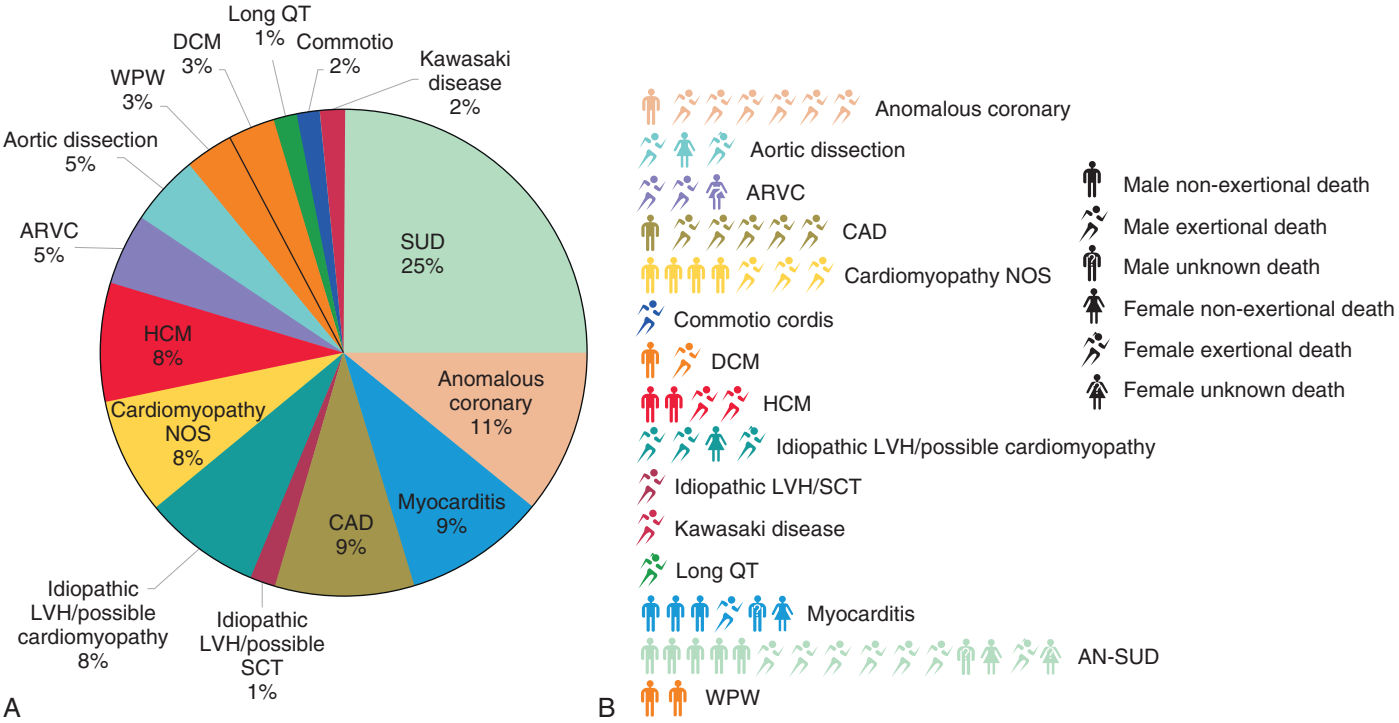

Fig. 485.1 A, Causes of sudden cardiac death in adolescent and young adult athletes. B, Cause and activity at time of death. One person figure equals one death; female figures follow male figures unless no male deaths were present. AN-SUD, Autopsy-negative sudden unexplained death; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; NOS, not otherwise specified; SCT, sickle cell trait; SUD, sudden unexplained death; WPW, Wolff-Parkinson-White syndrome. *(From Harmon KG, Asif I, Maleszewski JJ, et al. Incidence, cause, and comparative frequency of sudden cardiac death in National Collegiate Athletic Association athletes. Circulation. 2015;132:10–19, Fig. 2.)*

CARDIOMYOPATHY

All three major types of cardiomyopathy (hypertrophic, dilated, and restrictive) are associated with sudden death in the pediatric population; cardiac arrest or sudden death may be the initial manifestation of the cardiomyopathy (see Chapter 488.1).

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the athletic adolescent in the United States. The annual risk of sudden death in young patients with HCM is 2% per year. Risk factors for sudden death include a history of syncope, symptoms, myocardial size, ventricular arrhythmias, and presentation at an early age. Many patients with HCM have left ventricular outflow tract obstruction (LVOTO). The mechanism of sudden death is arrhythmic and may be secondary to the development of dynamic obstruction with exercise and resultant loss of cardiac output, or may be related to cardiac ischemia. Thus patients without LVOTO are also at risk of sudden death. The **dilated cardiomyopathies** are also associated with SCD in children, although the risk is clearly lower than in adults.

Arrhythmogenic cardiomyopathy (also referred to as *arrhythmogenic right ventricular cardiomyopathy*) is a specific form of cardiomyopathy associated with exercise-induced ventricular arrhythmias and sudden death. It mainly affects the right ventricle, but the left can be involved as well. The diagnosis can be difficult; MRI, electrophysiology study, or endomyocardial biopsy is used with limited reliability. Pathologically, the disease is characterized by transmural fatty replacement of right ventricular myocardium, with patchy areas of fibrosis. Pathogenic variants are noted in ~60% of this autosomal dominant (with incomplete penetrance) disorder; associated genes include *PKP2, DSP, DSC2, DSG2, JUP, CTNNA3, PLN, TMEN43, SCN5A, CDH2,* and *DES*.

Myocarditis has often been found on pathology of patients with sudden death of unknown etiology. Symptoms before sudden death may be absent or may include overt heart failure or subtle findings such as a high heart rate. Pediatric patients with this disease may have complete atrioventricular block or ventricular arrhythmias.

Table 485.1 Potential Causes of Sudden Death in Infants, Children, and Adolescents

SIDS AND SIDS "MIMICS"
SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent CHD
CORRECTED OR UNOPERATED CHD
Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left heart syndrome
Eisenmenger syndrome
CORONARY ARTERIAL DISEASE
Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
AORTOPATHIES (DISSECTION, RUPTURED AORTA)
Marfan syndrome
Loeys-Dietz syndrome
Takayasu aortitis
Smooth muscle dysfunction syndrome
Vascular Ehlers-Danlos syndrome
Familial thoracic aortic aneurysm and dissection syndrome
Mycotic aneurysm
MYOCARDIAL DISEASE
Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic (right ventricular) cardiomyopathy
Lyme carditis
Takotsubo syndrome
Nonischemic left ventricular scar
Myocardial infarction
CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Wolff-Parkinson-White syndrome
Complete AV block
Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic (right ventricular) cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor
MISCELLANEOUS
Seizures
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

*Common.
CHD, Congenital heart disease; SIDS, sudden infant death syndrome.

CARDIAC ARRHYTHMIA

A primary conduction system abnormality may result in sudden death. Causes include Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, short QT syndrome, and Brugada syndrome. Besides causing supraventricular tachycardia, **WPW syndrome** can result in atrial fibrillation with rapid conduction across the accessory pathway, leading to VF and sudden death (Fig. 485.2). This is unusual in pediatric patients but has an increasing incidence in adolescence. In adults, there is an incidence of sudden death in asymptomatic patients of 1 per 1,000 patient-years, but this rate may well be higher in children, who have not yet survived to adulthood. As digoxin and verapamil can augment conduction down accessory pathways, these drugs are contraindicated in WPW syndrome.

Long QT syndrome (LQTS; see Chapter 484), a group of channelopathies that affect ventricular repolarization, is also associated with sudden death (Fig. 485.3). The mechanism of sudden death is polymorphic ventricular tachycardia **(torsades de pointes)** (Fig. 485.4). An initial presentation of SCD is found in 9% of patients. Thus treatment of asymptomatic patients with a long QT interval on electrocardiogram (ECG) and positive family history is advised.

Acquired long QT interval may be seen in patients with marked electrolyte abnormalities, central nervous system injury, or starvation (including bulimia and anorexia nervosa). Medications can also result in prolongation of the QT interval (see Table 484.4). These patients are also at risk of malignant ventricular arrhythmias, and correction of the underlying problem or withdrawal of the inciting medication may be necessary to reduce the risk of sudden death.

Brugada syndrome, an autosomal dominant disorder associated with SCD, often occurs with fever, drugs, nighttime electrolyte disorders, or after a large meal (Fig. 485.5). The most common pathogenic variant is a loss of function in *SCN5A,* seen in up to 30% of patients. Typical ECG findings include *coved* ST segment elevations in leads V_1-V_3; death results from either VF or ventricular tachycardia.

MISCELLANEOUS CAUSES

Commotio cordis is an often fatal condition that follows blunt nonpenetrating trauma to the chest (e.g., from a baseball or hockey puck). Occasionally, innocent-appearing chest blows incurred at home or at a playground may be fatal. Patients experience immediate VF in the absence of identifiable cardiac trauma (contusion, hematoma, lacerated coronary artery). This risk is highest in children before adolescence. Historically, death results from VF that is unresponsive to resuscitative efforts in 85–90% of children. Immediate direct current (DC) defibrillation may be effective, if available, particularly if employed

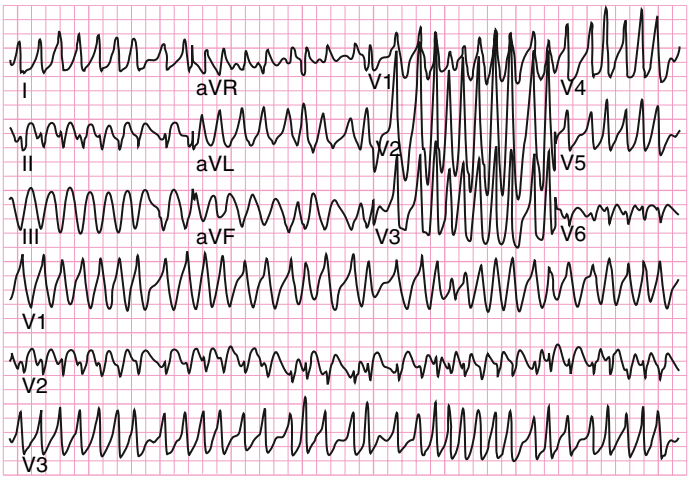

Fig. 485.2 Atrial fibrillation in a patient with Wolff-Parkinson-White syndrome and rapid conduction to the ventricle. Note the wide QRS complexes, a result of full preexcitation, and the irregularly irregular ventricular response, caused by the atrial fibrillation.

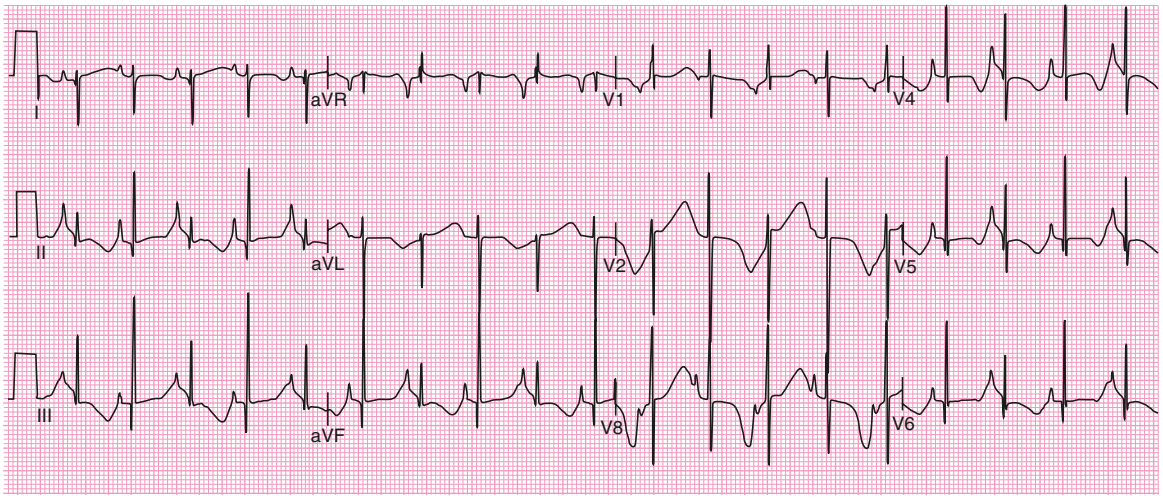

Fig. 485.3 Long QT syndrome in a neonate. QTc is markedly prolonged, and T-wave alternans is evident.

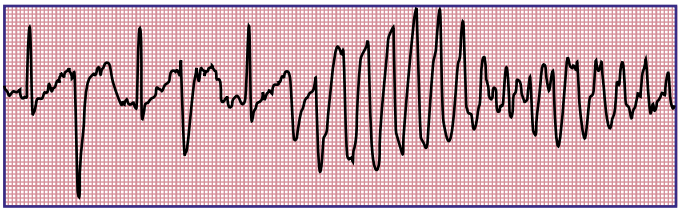

Fig. 485.4 Episode of torsades de pointes in a patient with long QT syndrome.

immediately; however, it is reported to be successful in only approximately 25% of cases.

EVALUATION AND THERAPY FOR RESUSCITATED PATIENTS

It is important to focus therapy on potentially reversible causes of sudden death. These include correction of major hemodynamic defects, pacing therapy for a patient with bradycardia, or supportive therapy for myocarditis. Unfortunately, reversible causes are not always found in young cardiac arrest survivors. Adding to this dilemma is the limited ability to predict antiarrhythmic drug response or risk of recurrence. The **implantable-cardioverter defibrillator** (ICD) is the therapy of choice for survivors of most forms of arrhythmic sudden death, with the exception of correctable causes such as WPW (see Chapter 484).

MEDICATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Concern has been raised that stimulant medications prescribed for children with attention-deficit/hyperactivity disorder might increase the risk of sudden death (see Chapter 50). The concern arises from a limited number of reports to the U.S. Food and Drug Administration (FDA) of sudden death of unknown etiology in individuals taking stimulant medications, mostly adults. In a few cases, left ventricular hypertrophy caused by hypertension, coarctation of the aorta, or HCM has been identified at postmortem examination. No prospective studies support the notion that these medications increase the risk, and there is no evidence that ECG screening will reliably identify a subgroup at risk. Some have suggested ECG screening of children before starting these medications, but there is no consensus that such an approach is effective. The current recommendations do not support ECG screening before the initiation of stimulant medication in the absence of a positive cardiac history.

PREVENTION OF SUDDEN DEATH

The probability of survival to hospital discharge for a young patient who experiences an out-of-hospital cardiac arrest is <20%. The

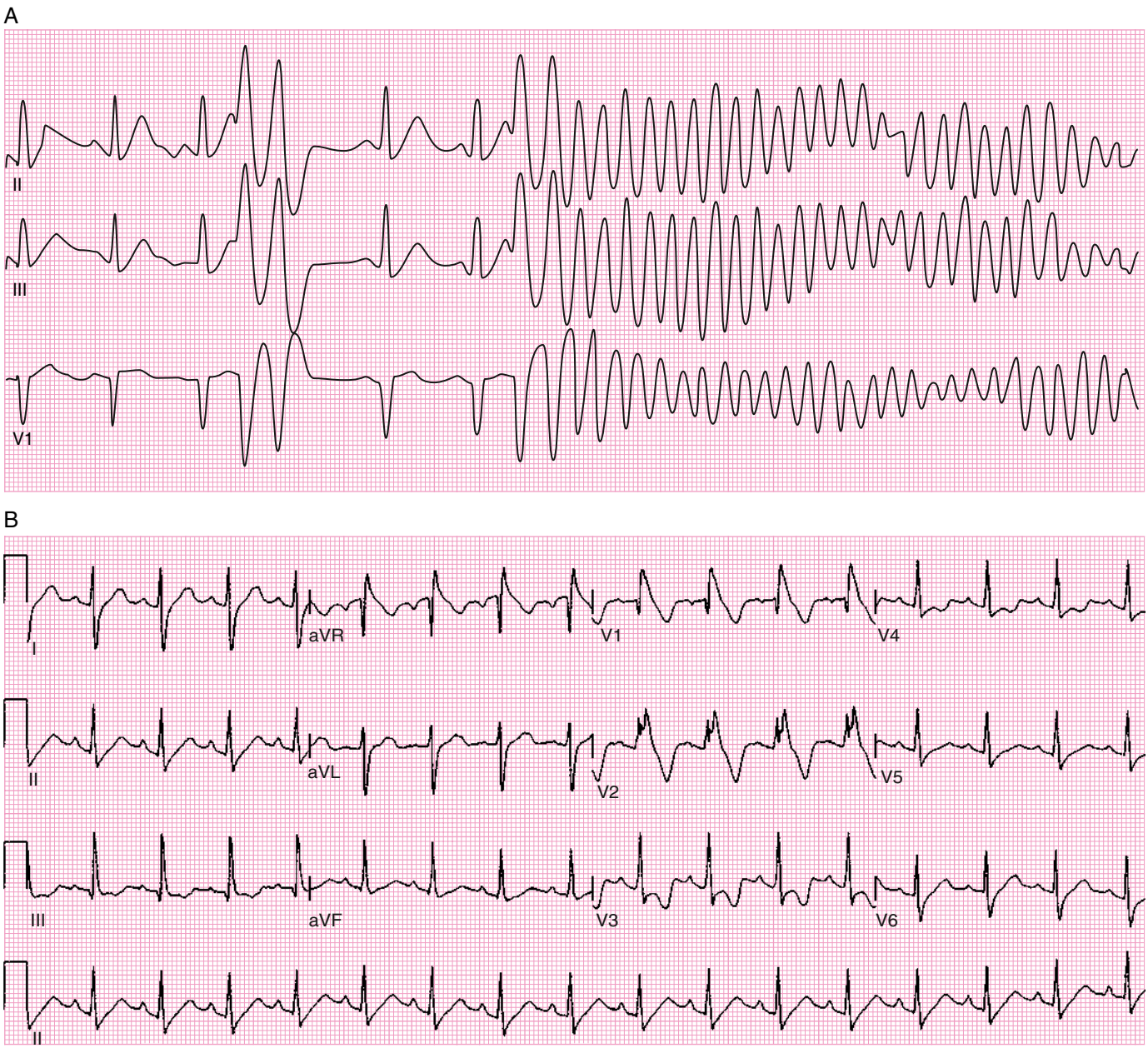

Fig. 485.5 Brugada syndrome. **A**, Frequent ventricular ectopy and sustained polymorphic ventricular tachycardia. **B**, Persistent coved-type ST segment elevation in lead V_1 and V_2 characteristic of Brugada type I. *(A from Talib S, van de Poll SE. Brugada syndrome diagnosed after Ramadan. Lancet. 2013;382:100.)*

presence of immediate **automatic external defibrillators** (AEDs), when combined with standard cardiopulmonary resuscitation (CPR) at the site of exercise (gym, track, basketball, or football arena), improves survival substantially. Thus identifying patients at risk is extremely important. The American Academy of Pediatrics Policy Statement on Sudden Death in the Young provides primary care providers with guidelines screening for life-threatening conditions, regardless of athletic status.

Some of the more common causes of sudden death in children and adolescents can be identified from the patient's history (prodromal symptoms), the family history, and physical examination. The American Heart Association (AHA) has a recommended 14-point preparticipation evaluation (PPE) that includes questions about personal and family history in addition to physical exam findings (Table 485.2). The screening for sudden cardiac arrest and SCD should be performed at the time of PPE or upon entry into middle school and high school. The AAP's Preparticipation Physical Evaluation form is available at https://www.aap.org/. Of paramount importance is the careful evaluation of any child who experiences **syncope** in association with **exercise** because this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Patient avoidance of high-risk behavior (cocaine use, anorexia nervosa) and knowledge of drug side effects or drug interactions and contraindications are critical. Chest-protecting equipment has not been shown to prevent commotio cordis. Prompt bystander CPR and rapid defibrillation with an AED has the highest chance of leading to survival. Family survivors of victims of sudden death should also be evaluated for genetic etiologies of SCD (e.g., LQTS, HCM).

The 14-element screening checklist underperforms and may miss high-risk cardiac lesion. Depending on the population (elite vs recreational athletes) and the screening protocol (checklist, with ECG, with echocardiogram, with cardiac MRI), the incidence of

Table 485.2 Fourteen-Element Cardiovascular Screening Checklist for Congenital and Genetic Heart Disease

PERSONAL HISTORY
1. Chest pain/discomfort/tightness/pressure related to exertion
2. Unexplained syncope/near-syncope: Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion
3. Excessive exertional and unexplained dyspnea/fatigue or palpitations, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
6. Prior restriction from participation in sports
7. Prior testing for the heart, ordered by a physician
FAMILY HISTORY
8. Premature death (sudden and unexpected, or otherwise) before age 50 attributable to heart disease in at least one relative
9. Disability from heart disease in close relative <50 yr of age
10. Hypertrophic or dilated cardiomyopathy, long QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of certain cardiac conditions in family members
PHYSICAL EXAMINATION
11. Heart murmur: Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction
12. Femoral pulses to exclude aortic coarctation
13. Physical stigmata of Marfan syndrome
14. Brachial artery blood pressure (sitting position): Preferably taken in both arms

From American College of Cardiology: ACC/AHA release recommendations for congenital and genetic heart disease screenings in youth. https://www.acc.org/latest-in-cardiology/articles/2014/09/15/14/24/acc-aha-release-recommendations-for-congenital-and-genetic-heart-disease-screenings-in-youth

at-risk cardiac lesions varies from 0.3–0.4% to 1.4%. The use of a preparticipation ECG for the detection of those athletes at risk for sudden death has long been controversial. Because many athletes either have no pre-event symptoms or are unwilling to admit to symptoms for concern of not being able to play, some have proposed that the ECG may identify a small but at-risk group with HCM or prolonged QT, Brugada, or WPW syndromes. These ECGs would fail to identify patients with phenotype-negative LQTS or catecholaminergic polymorphic ventricular tachycardia, as well as coronary artery anomalies. In addition, many false positives may be identified, requiring further evaluation to exclude worrisome diagnoses. Preparticipation ECG testing is mandatory in several European countries but not in the United States, although many athletic groups with varsity-level or professional membership (e.g., collegiate or professional sports organizations) require such testing as part of the medical evaluation. If the ECG is abnormal, **echocardiography** is performed. Cost-effectiveness studies suggest that the cost for implementation of a national program in the United States would be prohibitive because of the low incidence of sudden death in the pediatric population, the high rate of false-positive ECGs, and the difficulty in definitively excluding cardiac disease in patients with borderline ECG findings. Although studies of regional or national screening programs have suggested some benefit (e.g., the Veneto region of Italy), others have failed to demonstrate any effect of screening on the background incidence of sudden death in young individuals.

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Section 5

Acquired Heart Disease

Chapter 486

Infective Endocarditis*

Erin Faherty and Thomas S. Murray

Infective endocarditis includes acute and subacute *bacterial* endocarditis, as well as *nonbacterial* endocarditis, caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The inability to eradicate infective endocarditis by prevention or early treatment stems from several factors. The disease represents a complex interplay between a pathogen and host factors such as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism changes over time; and diagnosis may be difficult during early stages and thus is often delayed until a more serious manifestation has developed. Special risk groups include intravenous drug users; survivors of cardiac surgery, especially those with mechanical prosthesis; patients taking immunosuppressant medications; and patients who require chronic intravascular catheters. Some patients have endocarditis on a native valve previously thought to be healthy but found to have mild structural abnormalities on surgical inspection.

ETIOLOGY

Viridans-type streptococci (α-hemolytic streptococci groups such as *Streptococcus mitis, S. anginosus, S. mutans, S. salivarius, S. bovis, S. sanguinis,* and *S. mitis*) and *Staphylococcus aureus* remain the leading causative agents for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently, and in approximately 6% of cases, blood cultures are negative for any organisms (Table 486.1). No relationship exists between the infecting organism and the type of congenital defect, duration of illness, or age of the child. Staphylococcal endocarditis is more common in patients with no underlying heart disease. Viridans group streptococcal infection is more common after dental procedures; enterococci are seen more often after lower bowel or genitourinary manipulation.

Pseudomonas aeruginosa or *Serratia marcescens* is seen more frequently in intravenous drug users, and fungal organisms are encountered after open heart surgery. Coagulase-negative staphylococci are common in the presence of an indwelling central venous catheter.

EPIDEMIOLOGY

Infective endocarditis is often a complication of congenital or rheumatic heart disease but can also occur in children without any abnormal valves or cardiac malformations. In developed countries, congenital heart disease (CHD) is the overwhelming predisposing factor. Endocarditis is rare in infancy; in this age-group it usually follows open heart surgery or is associated with a central venous line.

Patients with congenital heart lesions where there is turbulent blood flow because of a hole or stenotic orifice, especially if there is a high-pressure gradient across the defect, are most susceptible to

* The authors would like to thank Dr Robert S. Baltimore for his work on previous editions of this chapter.

Table 486.1 Bacterial Agents in Pediatric Infective Endocarditis

COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Viridans group streptococci *(S. mutans, S. sanguinis, S. mitis)*
Staphylococcus aureus
Group D streptococcus (enterococcus) *(S. bovis, S. faecalis)*
UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS
Streptococcus pneumoniae
Haemophilus influenzae
Coagulase-negative staphylococci
Abiotrophia defectiva (nutritionally variant streptococcus)
*Coxiella burnetii (Q fever)**
Neisseria gonorrhoeae
*Brucella**
*Chlamydia psittaci**
*Chlamydia trachomatis**
*Chlamydia pneumoniae**
Legionella*
Bartonella*
*Tropheryma whipplei** (Whipple disease)
HACEK group†
*Streptobacillus moniliformis**
*Pasteurella multocida**
Campylobacter fetus
Culture negative (6% of cases)
PROSTHETIC VALVE
Staphylococcus epidermidis
Staphylococcus aureus
Viridans group streptococcus
Pseudomonas aeruginosa
Serratia marcescens
Diphtheroids
*Legionella spp.**
HACEK group†
Fungi‡

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for >7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.
†The HACEK group includes Haemophilus spp. (H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella spp.
‡Candida spp., Aspergillus spp., Pseudallescheria boydii, Histoplasma capsulatum.

endocarditis. This turbulent flow traumatizes the vascular endothelium, creating a substrate for deposition of fibrin and platelets, leading to the formation of a *nonbacterial thrombotic embolus (NBTE)* that is thought to be the initiating lesion for infective endocarditis. Biofilm forms on the surface of implanted mechanical devices such as valves, catheters, or pacemaker wires, which also serves as the adhesive substrate for infection. The development of transient bacteremia then colonizes this NBTE or biofilm, leading to proliferation of bacteria within the lesion. Bacterial surface proteins, such as the FimA antigen in viridans streptococci, act as adhesion factors to the NBTE or biofilm, after which bacteria can rapidly proliferate within the vegetation. Given the heavy colonization of mucosal surfaces (the oropharynx or gastrointestinal, vaginal, or urinary tracts) by potentially pathogenic bacteria, these surfaces are thought to be the origin of this transient bacteremia. There is controversy over the extent to which daily activities (e.g., brushing or flossing the teeth) vs invasive procedures (e.g., dental cleaning or surgery) contribute to this bacteremia. Transient bacteremia is reported to occur in 20–68% of patients after tooth brushing and flossing, and even in 7–51% of patients after chewing food. The magnitude of this bacteremia is also similar to that resulting from dental procedures. Maintenance of good oral hygiene may be a more important factor in decreasing the frequency and magnitude of bacteremia. Case reports suggest that body piercing and tattoos may be additional risk factors.

Children at **highest risk** of adverse outcome after infective endocarditis include those with prosthetic cardiac valves or other prosthetic material used for cardiac valve repair, unrepaired cyanotic CHD (including those palliated with shunts and conduits), completely repaired defects with prosthetic material or device during the first 6 months after repair, repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or device, valve stenosis or insufficiency occurring after heart transplantation, permanent valve disease from **rheumatic fever** (mitral stenosis, aortic regurgitation), and previous infective endocarditis. Patients with high-velocity blood flow lesions such as ventricular septal defects (VSDs) and aortic stenosis are also at high risk. In older patients, congenital bicuspid aortic valves and mitral valve prolapse with regurgitation pose additional risks for endocarditis. Surgical correction of CHD may reduce but does not eliminate the risk of endocarditis, except for the repair of a simple atrial septal defect or patent ductus arteriosus without prosthetic material.

In ~30% of patients with infective endocarditis, a predisposing factor is presumably recognized. Although a preceding dental procedure may be identified in 10–20% of patients, the time of the procedure may range from 1 to 6 months before the onset of symptoms—thus the continued controversy over the absolute risk of infective endocarditis after dental procedures. Primary bacteremia with *S. aureus* is thought to be another risk for endocarditis. The occurrence of endocarditis directly after most routine heart surgery is relatively low, but it can be an antecedent event, especially if prosthetic material is used. In the small group of patients with culture-negative endocarditis, epidemiologic or exposure factors may contribute to the diagnosis (Table 486.2).

CLINICAL MANIFESTATIONS

Table 486.3 outlines the manifestations of infective endocarditis. Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except occasionally weight loss) that persists for as long as several months may be the only symptom. Alternatively, with pathogenic organisms such as *S. aureus,* the onset may be acute and severe, with high intermittent fever and prostration. Usually, the onset and course vary between these two extremes. Fever in the absence of signs of URI in a patient with congenital heart disease must be considered as endocarditis. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and at times chills, nausea, and vomiting. The cardiac examination often depends on the underlying heart disease and the location of infection. A new pathologic murmur or changing heart murmur may be appreciated and can be associated with heart failure. Of note, children with palliated congenital heart disease, such as those palliated with a shunt, may not present with a change in murmur. Splenomegaly and petechiae are seen in <50% of patients. Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated with staphylococcal disease and may be late manifestations. Meningismus, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications. Meningitis may be seen together with pneumococcal endocarditis. Myocardial abscesses may occur with staphylococcal disease and may damage the cardiac conducting system, causing heart block, or may rupture into the pericardium and produce purulent pericarditis. Pulmonary (with right-sided endocarditis) and systemic emboli (with left-sided lesions) are infrequent, except with fungal disease.

Many of the classic **skin findings** develop late in the disease; they are seldom seen in appropriately treated patients. Such manifestations include **Osler nodes** (tender, pea-size intradermal nodules in the pads of the fingers and toes), **Janeway lesions** (painless, small,

Table 486.2 Epidemiologic Clues in the Etiologic Diagnosis of Culture-Negative Endocarditis

EPIDEMIOLOGIC FEATURE	COMMON MICROORGANISM
Injection drug use (IDU)	*Staphylococcus aureus,* including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus* Coagulase-negative staphylococci Fungi Aerobic gram-negative bacilli *Corynebacterium* spp.
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus spp.* Group B streptococci *(S. agalactiae)* *Listeria monocytogenes* Aerobic gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S. aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci Nutritionally variant streptococci *Abiotrophia defectiva* *Granulicatella* spp. *Gemella* spp. HACEK organisms
Alcohol use, cirrhosis	*Bartonella spp.* *Aeromonas spp.* *Listeria spp.* *Streptococcus pneumoniae* *β-Hemolytic* streptococci
Burns	*S. aureus* Aerobic gram-negative bacilli, including *P. aeruginosa* Fungi
Diabetes mellitus	*S. aureus* β-Hemolytic streptococci *S. pneumoniae*
Early (≤1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Aerobic gram-negative bacilli Fungi *Corynebacterium* spp. *Legionella* spp.
Late (>1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* *Viridans group streptococci* *Enterococcus* spp. Fungi *Corynebacterium* spp.
Dog or cat exposure	*Bartonella spp.* *Pasteurella spp.* *Capnocytophaga spp.*
Contact with contaminated milk or infected farm animals	*Brucella spp.* *Coxiella burnetii* *Erysipelothrix spp.*
Homeless, body lice	*Bartonella spp.*
HIV/AIDS	*Salmonella spp.* *S. pneumoniae* *S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid-organ transplantation	*S. aureus* *Aspergillus fumigatus* *Enterococcus spp.* *Candida spp.*
Gastrointestinal lesions	*Streptococcus gallolyticus (bovis)* *Enterococcus spp.* *Clostridium septicum*

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp.; HIV/AIDS, human immunodeficiency virus infection and acquired immunodeficiency syndrome.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. *Circulation.* 2015;132:1435–1486.

erythematous, or hemorrhagic lesions on the palms and soles), and **splinter hemorrhages** (linear lesions beneath the nails). These lesions may represent vasculitis produced by circulating antigen-antibody complexes. Retinal lesions are seen in 10–20%.

In the newborn infant the major risk factor for infective endocarditis is the presence of a central intravenous line. Thus prematurity is a risk, as are other severe congenital abnormalities. CHD is less likely to be the underlying condition than it is for older children. The clinical conditions are variable and may be indistinguishable from sepsis or congestive heart failure. Identification of infective endocarditis is most often based on a high index of suspicion during evaluation of an infection in a child with an underlying risk factor.

DIAGNOSIS

The critical information for appropriate treatment of infective endocarditis is obtained from blood cultures. All other laboratory data are secondary in importance (see Table 486.3). Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings. Although increased blood volume can increase the sensitivity of the blood culture, smaller volumes are reasonable in neonates and small children. When small volumes of blood are present, a single aerobic blood culture bottle should be inoculated. Ideally, for patients weighing 2-12.7 kg, the volume of the first blood culture is 4 mL (repeat culture is 2 mL); for patients 12.8-36.3 kg it is 10 mL for initial and repeat, and for patients >36.3 kg, 20-30 mL for both. Three to five separate blood collections should be obtained after careful preparation of the phlebotomy site. Contamination presents a special problem because bacteria found on the skin may cause infective endocarditis. The timing of collections is not important because bacteremia can be expected to be relatively constant. In 90% of cases of endocarditis, the causative agent is recovered from the first two blood cultures. Bacteremia is low grade in 80% (<100 colony-forming units/mL of blood). The laboratory should be notified that endocarditis is suspected so that, if necessary, the blood can be cultured on enriched media for longer than usual (>5 days) to detect nutritionally deficient and fastidious bacteria or fungi.

Table 486.3 Manifestations of Infectious Endocarditis

HISTORY
Prior congenital or rheumatic heart disease
Preceding dental, urinary tract, or intestinal procedure
Intravenous drug use
Central venous catheter
Prosthetic heart valve
SYMPTOMS
Fever
Chills
Chest and abdominal pain
Arthralgia, myalgia
Dyspnea
Malaise, weakness
Night sweats
Weight loss
CNS manifestations (stroke, seizures, headache)
SIGNS
Elevated temperature
Tachycardia
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)
Janeway lesions
New or changing murmur
Splenomegaly
Arthritis
Heart failure
Arrhythmias
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)
Clubbing
LABORATORY STUDIES
Positive blood culture
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure
Elevated C-reactive protein
Anemia
Leukocytosis
Immune complexes
Hypergammaglobulinemia
Hypocomplementemia
Cryoglobulinemia
Rheumatoid factor
Hematuria
Renal failure: azotemia, high creatinine (glomerulonephritis)
Chest radiograph: bilateral infiltrates, nodules, pleural effusions
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, or new-onset valve insufficiency

CNS, Central nervous system.

Table 486.4 Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
Brucella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Coxiella burnetii	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and mNGS of surgical material or blood/plasma
Bartonella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Chlamydia spp.	Serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Mycoplasma spp.	Serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Legionella spp.	Blood cultures; serology; culture, immunohistology, and mNGS of surgical material or blood/plasma
Tropheryma whipplei	Histology and mNGS of surgical material or blood/plasma

IgG, Immunoglobulin G; mNGS, metagenomic next-generation sequencing; PCR, polymerase chain reaction
From Moreillon P, Que YA. Infective endocarditis *Lancet*. 2004;363:139–148.

Although bacteremia may occur in the absence of endocarditis, bacteremia secondary to *S. mutans, S. bovis I*, *S. mitis, S. sanguinis,* and *S. aureus* (in the absence of focal musculoskeletal infection) is highly concerning for endocarditis. Antimicrobial pretreatment of the patient reduces the yield of blood cultures by 50–60%. Other specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses, and in the presence of manifestations of meningitis, cerebrospinal fluid. Serologic diagnosis or metagenomic next-generation sequencing or polymerase chain reaction for 16S and 28S ribosomal RNA (rRNA) for bacteria and fungi, respectively, of resected valve tissues is necessary in patients with unusual or fastidious microorganisms when there is suspicion of culture-negative endocarditis or if the patient has received prior antibiotics (Table 486.4 and Fig. 486.1). Metagenomic next-generation sequencing on blood and plasma may help identify pathogens in patients with culture-negative endocarditis. Suspicion should be high when evaluating infection in a child with an underlying contributing factor.

Echocardiography remains the mainstay of diagnosis. Two-dimensional echocardiography can identify the size, shape, location, and mobility of the lesion; when combined with Doppler interrogation, the presence of valve dysfunction (regurgitation, obstruction) can be determined. (Fig. 486.2). In pediatric patients, transthoracic echocardiogram is usually adequate for detection of lesions, especially for children <60 kg. Transesophageal echocardiogram should be considered in pediatric patients with limited transthoracic views; it is superior to transthoracic echocardiogram in evaluating prosthetic valves or complications of infective endocarditis, such as aortic root abscess. Intracardiac echocardiography can be useful for patients with suspicion for an infected pacemaker lead or implanted percutaneous pulmonary valve. Cardiac MRI may be useful in suspected perivalvular complications, and PET-CT may aid in the diagnosis of endocarditis for those patients with prosthetic valves.

Echocardiography may also be helpful in predicting embolic complications, given that lesions >1 cm and fungating masses are at greatest risk for embolization. The absence of vegetations does not exclude endocarditis, and vegetations are often not visualized in the early phases of the disease or in patients with complex congenital heart lesions. Electrocardiography should be part of the evaluation and can demonstrate new rhythm disorders such as **ventricular**

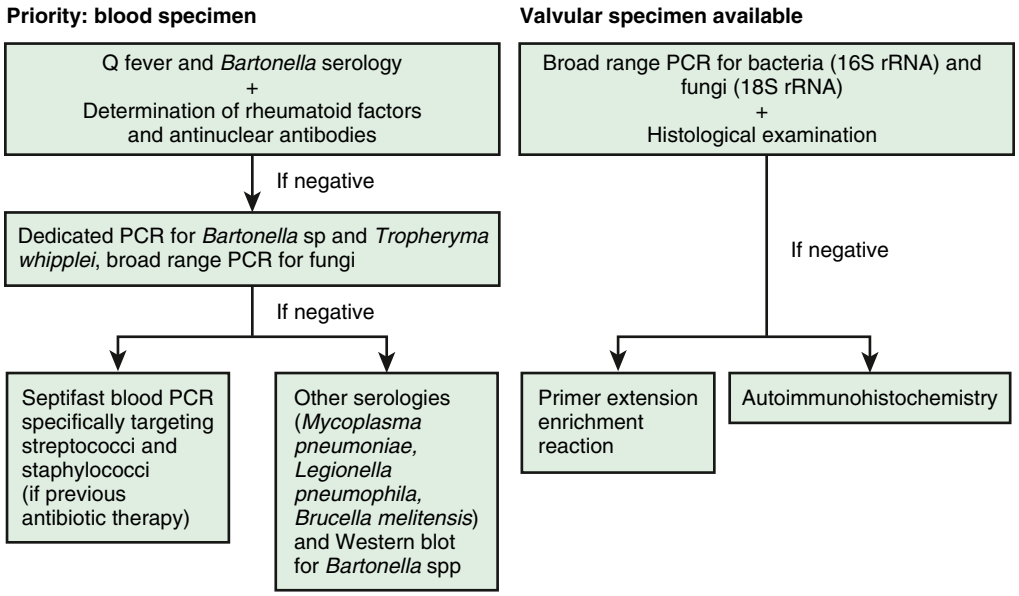

Fig. 486.1 Algorithm of diagnostic tests applied to clinical specimens for the identification of the causative agents of **blood culture–negative endocarditis**. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor be routinely done for the diagnosis of noninfective endocarditis. *(From Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet. 2012;379:965–975, Fig. 2.)*

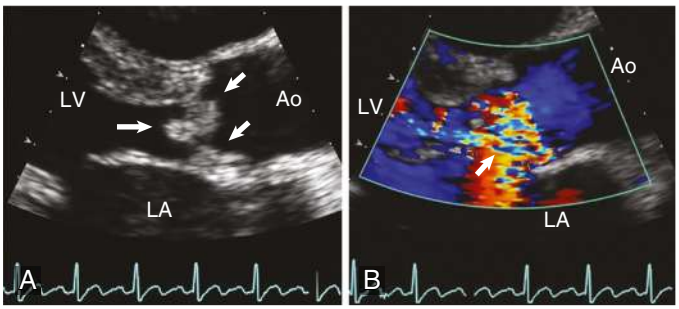

Fig. 486.2 Infective endocarditis of the native aortic valve. **A,** Transthoracic echocardiography shows vegetations *(small arrows)* attached to the left ventricular aspects of the valve cusps and prolapsing into the left ventricular outflow tract *(large arrow)* during diastole. **B,** Severe aortic regurgitation *(arrow)* is shown by color Doppler. Ao, Ascending aorta; LA, left atrium; LV, left ventricle. *(From Baddour LM, Freeman WK, Suri RM, Wilson WR. Cardiovascular infections. In: Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019: Fig. 73-1, p. 1490.)*

ectopy and conduction disorders such as **complete heart block**. The presence of either of these findings, particularly heart block, may signal a serious or even life-threatening complication of endocarditis.

The **Duke criteria** help in the diagnosis of endocarditis (Table 486.5). Two major criteria, one major and three minor, or five minor criteria suggest definite endocarditis. Additional minor criteria to those listed include newly diagnosed clubbing, splenomegaly, splinter hemorrhages, or petechiae; high erythrocyte sedimentation rate or C-reactive protein level; presence of central nonfeeding or peripheral lines; and microscopic hematuria.

PROGNOSIS AND COMPLICATIONS

Despite the use of antibiotic agents, mortality remains high, up to 25%. Serious morbidity occurs in 50–60% of children with documented infective endocarditis; the most common is heart failure caused by worsening valvular regurgitation due to aortic or mitral valve vegetations, accompanied by ventricular dysfunction. Myocardial abscesses and toxic myocarditis may also lead to heart failure without characteristic changes in auscultatory findings and, occasionally, to life-threatening arrhythmias. Systemic emboli, often with central nervous system manifestations, are a major threat. Pulmonary emboli may occur in children with VSD or tetralogy of Fallot, although massive life-threatening pulmonary embolization is rare. Other complications include mycotic aneurysms, rupture of a sinus of Valsalva, obstruction of a valve secondary to large vegetations, acquired VSD, and heart block as a result of involvement (abscess) of the conduction system. Additional complications include meningitis, osteomyelitis, arthritis, renal abscess, purulent pericarditis, and immune complex–mediated glomerulonephritis.

TREATMENT

Antibiotic therapy should be instituted immediately once a definitive diagnosis of infectious endocarditis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. The choice of antibiotics, method of administration, and length of treatment should be coordinated with consultants from both cardiology and infectious diseases (Tables 486.6 and 486.7). Empirical therapy after appropriate blood cultures are drawn but before the identifiable agent is recovered may be initiated with vancomycin plus gentamicin in patients without a prosthetic valve and when there is a high risk of *S. aureus,* enterococcus, or viridans streptococci (the three most common organisms). High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Between 5 and 20 times the in vitro minimal inhibitory concentration must be produced at the site of infection to destroy bacteria growing at the core of these lesions. Several weeks are required for a vegetation to organize completely; therapy must be continued through this period so that recrudescence can be avoided. A total of 4-6 weeks of treatment is usually recommended. Depending on the clinical and laboratory responses, antibiotic therapy may require modification, and some patients require more

Table 486.5 Definition of Infective Endocarditis (IE): Modified Duke Criteria

DEFINITE INFECTIVE ENDOCARDITIS

Pathologic Criteria

- Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; *or*
- Pathologic lesions; vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis

Clinical Criteria

- Two major criteria, *or*
- One major criterion and three minor criteria, *or*
- Five minor criteria

Possible Infective Endocarditis

- One major criterion and one minor criterion, *or*
- Three minor criteria

Rejected Diagnosis of Infective Endocarditis

- Firm alternative diagnosis explaining evidence of suspected IE, *or*
- Resolution of IE syndrome with antibiotic therapy for ≤4 days, *or*
- No evidence of IE at surgery or autopsy, on antibiotic therapy for ≤4 days, *or*
- Does not meet criteria for possible IE

DEFINITION OF TERMS USED IN MODIFIED DUKE CRITERIA

Major Criteria

- Blood culture findings positive for IE
  Typical microorganisms consistent with IE from two separate blood cultures:
  - Viridans streptococci, *Streptococcus gallolyticus* (formerly known as *S. bovis*), *Staphylococcus aureus,* HACEK group, *or*
  - Community-acquired enterococci, in the absence of a primary focus, *or*

  Microorganisms consistent with IE from persistently positive blood culture findings, defined as:
  - At least two positive culture findings of blood samples drawn >12 hr apart, *or*
  - Three or most of at least four separate culture findings of blood (with first and last sample drawn ≥1 hr apart)
  - Single positive blood culture for *Coxiella burnetii* or anti–phase I IgG titer ≥1:800
- Evidence of endocardial involvement
  Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least *possible* IE by clinical criteria or *complicated* IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, *or*
  - Abscess, *or*
  - New partial dehiscence of prosthetic valve

  New valvular regurgitation; worsening or changing of preexisting murmur not sufficient

Minor Criteria

- Predisposition, predisposing heart condition, or intravenous drug use
- Fever—temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted earlier (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

TEE, Transesophageal echocardiography; TTE, transthoracic echocardiography.
Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633.

prolonged treatment. With highly sensitive viridans group streptococcal infections, shortened regimens that include oral penicillin for some portion have been recommended for certain adults, but effectiveness studies in children are lacking. In *nonstaphylococcal* disease, bacteremia usually resolves in 24-48 hours, whereas fever resolves in 5-6 days with appropriate antibiotic therapy. Resolution with *staphylococcal* disease takes longer.

If the infection occurs on a valve and induces or increases symptoms and signs of heart failure, appropriate therapy should be instituted, including diuretics, inotropic medications, and afterload reducing agents. Surgical intervention for infective endocarditis is indicated for severe aortic, mitral, or prosthetic valve involvement with intractable heart failure (Table 486.8). Severe heart failure may be associated with acute valve regurgitation, obstruction of conduits or shunts, or periannular extension of infection, including fistula formation. Rarely, a mycotic aneurysm, rupture of an aortic sinus, intraseptal abscess causing complete heart block, or dehiscence of an intracardiac patch requires emergency surgery. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels in 7-10 days in the absence of extracardiac infection, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Vegetations (aortic, mitral, prosthetic valve) >10-15 mm are at high risk of embolism. Although antibiotic therapy should be administered for as long as possible before surgical intervention, active infection is not a contraindication if the patient is critically ill as a result of severe hemodynamic deterioration from infective endocarditis. Emergent surgical intervention in patients with severe heart failure may improve the likelihood of survival. Removal of vegetations and, in some instances, valve replacement may be lifesaving, and sustained antibiotic administration will most often prevent reinfection. Replacement of infected prosthetic valves carries a higher risk.

Fungal endocarditis is difficult to manage and has a poorer prognosis. It has been encountered after cardiac surgery, in severely debilitated or immunosuppressed patients, and in patients on a prolonged course of antibiotics. The drugs of choice are amphotericin B (liposomal or standard preparation) and 5-fluorocytosine. Surgery to excise infected tissue is occasionally attempted, but often with limited success. Recombinant tissue plasminogen activation may help lyse intracardiac vegetations and avoid surgery in some high-risk patients.

PREVENTION

The American Heart Association (AHA) recommendations for antimicrobial prophylaxis before dental and other surgical procedures has resulted in a substantial reduction in the number of patients who require prophylactic treatment, and the procedures requiring coverage were recommended. The primary reasons for these revised recommendations were that (1) infective endocarditis is much more likely to result from exposure to the more frequent random bacteremias associated with daily activities than from a dental or surgical procedure, (2) routine prophylaxis may prevent "an exceedingly small" number of cases, and (3) the risk of antibiotic-related adverse events exceeds the benefits of prophylactic therapy. Improving general dental hygiene was thought to be a more important factor in reducing the risk of infective endocarditis resulting from routine daily bacteremias. The current recommendations limit the use of prophylaxis to those patients with cardiac conditions associated with the greatest risk of an adverse outcome from infective endocarditis (Table 486.9). Patients with permanently damaged valves from rheumatic heart disease should also be considered for prophylaxis. Prophylaxis for these patients is recommended for "all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa." Furthermore, "placement of removable prosthodontic or endodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa" are not indications for

Table 486.6 Therapy of Pediatric Native Valve Endocarditis Caused by Highly Penicillin-Susceptible[^] Viridans Group Streptococci and *Streptococcus bovis*

REGIMEN	DOSAGE*† AND ROUTE	DURATION	COMMENTS
Penicillin G	200,000-300,000 U/kg/24 hr IV given every 4 hr up to 12-24 million U/day	4 wk	Avoids nephrotoxicity of gentamicin
Or			
Ceftriaxone sodium	100 mg/kg/24 hr IV given every 12 hr **or** 80 mg/kg/24 hr given every 24 hr up to 4 g/day (If total amount is over 2 g/day then dosing should be every 12 hr)	4 wk	Avoids nephrotoxicity of gentamicin
Or			
Vancomycin hydrochloride¶	40 mg/kg/24 hr IV given every 8-12 hr up to 2g/day	4 wk	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain a trough concentration range of 10-15 μg/mL

[^]Defined as minimum inhibitory concentration (MIC) ≤0.10 μg/mL.
*Dosages recommended are for patients with normal renal function.
†Pediatric dose should not exceed that of a normal adult.
¶Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine release and facial flushing. Peak vancomycin levels should only be obtained to calculate the area under the curve to mean MIC ratio.
Data from Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update. A scientific statement from the American Heart Association. *Circulation.* 2015;132:1487–1515.

Table 486.7 Therapy for Pediatric Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE*§ AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin† ± gentamicin‡ for first 3-5 days	200 mg/kg/24 hr IV given every 4-6 hr up to 12 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV every 8 hr	4-6 wk	Clinical benefit of aminoglycosides has not been established. Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
For penicillin-allergic (non-anaphylactoid-type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin ± gentamicin‡ for first 3-5 days	100 mg/kg/24 hr IV given every 8 hr up to 12 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	4-6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.§ Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
OXACILLIN-RESISTANT STRAINS			
Vancomycin¶ ± gentamicin‡ for first 3-5 days	40 mg/kg/24 hr IV given every 8-12 hr up to 2 g/day AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	6 wk	Adjust vancomycin dosage to achieve trough concentration of 10-15 μg/mL. Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).
Daptomycin ± gentamicin‡ for first 3-5 days	6 mg/kg/24 hr given every 24 hr <6 yr of age; 10 mg/kg/24 hr given every 24 hr AND consider gentamicin 3-6 mg/kg/24 hr IV given every 8 hr	4-6 wk	Gentamicin trough levels of <1-2 μg/mL should be targeted to avoid risk of toxicity. Gentamicin peak levels should be obtained 30 min after the completion of an infusion with a peak goal of 3-5 μg/mL (for synergy).

*Dosages recommended are for patients with normal renal function.
§Pediatric dose should not exceed that of a normal adult.
†Penicillin G 200,000-300,000 U/kg/24 hr IV given every 4 hr up to 12-24 million U/day may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.
‡Gentamicin should be administered in close temporal proximity to nafcillin, or oxacillin dosing and blood levels monitored to reduce the risk of nephrotoxicity and ototoxicity.
¶For specific dosing adjustment and issues concerning vancomycin, see Table 464.6 footnotes.
IE, Infective endocarditis; IV, intravenously.
Data from Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update. A scientific statement from the American Heart Association. Circulation. 2015;132:1487–1515.

Table 486.8 Echocardiographic Features that Suggest Potential Need for Surgical Intervention

VEGETATION
Persistent vegetation after systemic embolization
Anterior mitral valve leaflet vegetation, particularly if it is highly mobile with size >10 mm*
One or more embolic events during the first 2 wk of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy*†
VALVULAR DYSFUNCTION
Acute aortic or mitral insufficiency with signs of ventricular failure†
Heart failure unresponsive to medical therapy†
Valve perforation or rupture†
PERIVALVULAR EXTENSION
Valvular dehiscence, rupture, or fistula†
New heart block†‡
Large abscess or extension of abscess despite appropriate antimicrobial therapy†

*Surgery may be required because of risk of embolization.
†Surgery may be required because of heart failure or failure of medical therapy.
‡Echocardiography should not be the primary modality used to detect or monitor heart block.
From Baddour LM, Freeman WK, Suri RM, et al. Cardiovascular infections. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier, 2019: Table 73-5, p. 1492.

Table 486.9 Cardiac Conditions Associated with Highest Risk of Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable (2007 AHA Statement)

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital heart disease (CHD)*
• Unrepaired cyanotic CHD, including palliative shunts and conduits
• Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 mo after the procedure†
• Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization)
• Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116:1736–1754.

prophylaxis. The 2023 recommendations of the European Society of Cardiology are noted in Table 486.10. Given that many invasive respiratory tract procedures do cause bacteremia, prophylaxis for many of these procedures is considered reasonable. In contrast to prior recommendations, prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases. Prophylaxis for patients undergoing cardiac surgery with placement of prosthetic material is still recommended. Given the highly individual nature of these recommendations, direct consultation with the child's cardiologist is still the best method for determining a specific patient's ongoing need for prophylaxis (Table 486.11).

Continuing education regarding both oral hygiene and, in appropriate cases, the need for prophylaxis is important, especially in teenagers and young adults. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of infective endocarditis.

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Table 486-10 2023 European Recommendations for Antibiotic Prophylaxis in Patients with Cardiovascular Diseases Undergoing Oro-Dental Procedures at Increased Risk of Infective Endocarditis

• Antibiotic prophylaxis is recommended in patients with previous IE.
• Antibiotic prophylaxis is recommended in patients with surgically implanted prosthetic valves and with any material used for surgical cardiac valve repair.
• Antibiotic prophylaxis is recommended in patients with transcatheter implanted aortic and pulmonary valvular prostheses.
• Antibiotic prophylaxis should be considered in patients with transcatheter mitral and tricuspid valve repair.
• Antibiotic prophylaxis is recommended in patients with untreated cyanotic CHD, and patients treated with surgery or transcatheter procedures with post-operative palliative shunts, conduits, or other prostheses. After surgical repair, in the absence of residual defects or valve prostheses, antibiotic prophylaxis is recommended only for the first 6 months after the procedure.

From Delgado V, Marsan NA, de Waha S, et al: 2023 ESC Guidelines for the Management of endocarditis. *Eur Heart J* 2023;193:1-95 https://doi.org/10.1093/eurheartj/ehad193.

Table 486.11 Prophylactic Antibiotic Regimens for a Dental Procedure (2007 AHA Statement)

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or* Cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*† *or* Clindamycin *or* Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† *or* Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM, Intramuscularly; IV, intravenously.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association *Circulation*. 2007;116:1736–1754.

Chapter 487

Rheumatic Heart Disease

Michael R. Carr and Stanford T. Shulman

Rheumatic involvement of the cardiac valves is the most important sequela of **acute rheumatic fever (ARF)**, and the second most common major manifestation after arthritis (see Chapter 229.1). The definitions of three subgroups of rheumatic heart disease (RHD) are noted in Table 487.1. The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of one or more of the heart valves. The mitral valve is affected most often, followed in frequency by the aortic valve. Isolated aortic valve disease is rare and generally seen with concomitant mitral valve involvement. Right-sided heart manifestations are rarer and are virtually only associated with left-sided valve disease. As the inflammation subsides, the verrucae tend to disappear and leave scar tissue. With repeated attacks of rheumatic fever, new verrucae form near the previous ones and the mural endocardium and chordae tendineae become involved. A single episode of **acute rheumatic carditis** often results in complete healing of the valvular lesions, whereas *repeated* episodes, especially involving previously affected valves, result in chronic **RHD**, which is the rationale for secondary prophylaxis. The prevalence of RHD ranges from 3 to 4 cases per 100,000 population in nonendemic countries to >1,000 cases per 100,000 in endemic countries (Fig. 487.1). On a global scale, the sequelae of RHD is significant, with up to 300,000 deaths per year related to the disease process, as well as an exponential degree of related comorbidity.

The diagnosis of ARF requires the fulfillment of the **Jones criteria** (see Chapter 229.1), with carditis being a major criterion. The diagnosis of RHD was once only based on cardiac auscultatory findings of mitral or aortic valve involvement, which was insensitive for early valve involvement/injury. This was based on valvulitis being seen more frequently in ARF compared with pericarditis or myocarditis, both of which lack more readily apparent physical examination findings. Screening large, high-risk populations with echocardiography demonstrated a substantially greater number of patients with RHD than those detected by auscultation alone. Because access to echocardiography is often available, the current version of the Jones criteria focused on the concept of **subclinical carditis (SCC)** detected by echocardiography (see Table 487.1). SCC is defined as echocardiographic evidence of mitral or aortic valvulitis in the absence of auscultatory findings and not consistent with physiologic mitral or aortic insufficiency (Table 487.2). Echocardiography with Doppler should be performed for all cases of confirmed or suspected ARF (Table 487.3). Additional recommendations are that echocardiography should be performed in moderate- to high-risk patient populations if ARF is considered likely and that echocardiography can be used to exclude cardiac findings consistent with ARF in patients with cardiac murmurs thought to be suggestive of rheumatic carditis. Additionally, serial echocardiography should be considered in patients with diagnosed or suspected ARF even if there is no evidence of valvulitis by echocardiography at diagnosis. The echocardiographic finding of SCC fulfills the major criterion for carditis. The category of latent RHD is another approach to include patients with mild asymptomatic valve changes not typically detected on physical exam but identified by screening high-risk populations with echocardiography (see Table 487.1).

PATTERNS OF VALVULAR DISEASE

Mitral Insufficiency

Mitral insufficiency is the result of structural changes that may include some loss of valvular substance and/or changes to the subvalvular apparatus, including elongation of the chordae, both of which can lead to valve dysfunction. During ARF with severe cardiac involvement, heart failure is caused by a combination of mitral insufficiency coupled with a pancarditis involving the pericardium and myocardium in addition to the endocardium/valve. Because of the increased volume load from the mitral insufficiency and the inflammatory process, the left ventricle dilates. The left atrium also enlarges to accommodate the regurgitant volume. Increased left atrial pressure results in pulmonary congestion and symptoms of left-sided heart failure. Spontaneous improvement often occurs with time, even in patients in whom mitral insufficiency is severe at the onset. The resultant chronic lesion is most often mild or moderate in severity, and the patient is often asymptomatic. More than half of patients with acute mitral insufficiency no longer have an audible mitral insufficiency murmur 1 year later, although they still may demonstrate insufficiency on echocardiography. In patients with severe chronic mitral insufficiency, pulmonary artery pressure (PAP) becomes elevated, the right ventricle and atrium become enlarged, and right-sided heart failure subsequently develops.

Clinical Manifestations

Physical signs of mitral insufficiency depend on its severity. With mild disease, signs of heart failure are not present, the precordium is quiet, and auscultation reveals a high-pitched **holosystolic murmur** at the apex that radiates to the axilla. With severe mitral insufficiency, signs of acute or chronic heart failure may be noted. The heart is enlarged, with a heaving apical left ventricular (LV) impulse and often an apical systolic **thrill**. The second heart sound (S_2) may be accentuated if pulmonary hypertension is present. A third heart sound or **gallop** is generally prominent. A holosystolic murmur is heard at the apex with radiation to the axilla. A short mid-diastolic rumbling murmur is caused by increased blood flow across the mitral valve as a result of the significant insufficiency. Therefore auscultation of a diastolic murmur, often referred to as **relative mitral stenosis (Carey-Coombs murmur)**, does not necessarily mean that true mitral stenosis is present. The latter lesion takes many years to develop and is characterized by a diastolic murmur of greater length, usually with presystolic accentuation.

The electrocardiogram and chest radiographs are normal if the mitral insufficiency is mild. With more severe insufficiency, the ECG shows a prominent, longer duration and often bifid P waves, signs of LV hypertrophy, and associated right ventricular (RV) hypertrophy if pulmonary hypertension is present. On chest radiograph, prominence of the left atrium and ventricle can be seen, the former of which is better seen on lateral projections. Congestion of the perihilar vessels, a sign of pulmonary venous hypertension, may also be evident. Calcification of the mitral valve is rare in children. Echocardiography in the acute phase may demonstrate enlargement of the left atrium and ventricle. LV systolic function can be impaired if there is also a component of myocardial inflammation. Mitral annular dilation, chordal elongation, and at times, evidence of chordal rupture resulting in a flail leaflet may be noted. The leaflet tips demonstrate a nodular appearance, and prolapse of the anterior mitral valve leaflet tip (much more often than the posterior leaflet) is seen. Doppler evaluation demonstrates the severity of the mitral regurgitation. Chronic mitral insufficiency from RHD is characterized on echocardiography by leaflet and chordal thickening, chordal fusion, and restricted leaflet motion. These changes often lead to stenosis, but poor coaptation of the abnormal leaflets can also lead to variable degrees of regurgitation. Cardiac catheterization and left ventriculography are considered only if diagnostic questions are not completely resolved by noninvasive assessment or in rare cases with a concern for significantly elevated PAP.

Complications

Severe mitral insufficiency may result in cardiac failure that may be precipitated by progression of the rheumatic process, recurrent episodes of ARF, the onset of **atrial fibrillation (AF)** or other arrhythmias, or infective endocarditis. The effects of chronic mitral insufficiency may become manifest after many years and include LV and RV failure and atrial and ventricular arrhythmias.

Treatment

In patients with mild mitral insufficiency, **prophylaxis** against recurrences of rheumatic fever is all that is required in addition to the typical treatment for ARF (Table 487.4). For more significant insufficiency, corticosteroids are added in the acute phase. Treatment of complicating heart failure (see Chapter 491), arrhythmias (see Chapter 484), and infective endocarditis (see Chapter 486) is described elsewhere. Afterload-reducing

agents—angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)—may reduce the regurgitant volume, attenuate pathologic compensatory mechanisms, and preserve LV function, but these have not been proven to alter the natural history of the disease process. Diuretics may also provide some symptomatic and clinical benefit in select cases. In rare cases, phosphodiesterase inhibitors such as milrinone may be used in the acute stage because of their inotropic, lusitropic, and systemic vascular dilating effects. Surgical treatment is indicated for patients who, despite adequate medical therapy, have persistent heart failure, dyspnea with moderate activity, and progressive cardiomegaly, often with pulmonary hypertension. Although annuloplasty and other forms of mitral valve repair provide good results in some children and adolescents, mitral valve replacement may be required, which can be more complicated in younger children. In patients with a prosthetic mitral valve replacement, prophylaxis against bacterial endocarditis is warranted for dental procedures, as the routine antibiotics taken by these patients for rheumatic fever prophylaxis are insufficient to prevent endocarditis. Additionally, current recommendations suggest selecting a different class of antibiotic for such procedures, rather than increasing the dose of the antibiotic taken for rheumatic fever prophylaxis. Lastly, it is important to remember that all attempts should be made at maximizing medical management of severe mitral insufficiency during the acute phase of the disease process, before considering surgical intervention, because surgery carries a poorer prognosis and an increased risk for reoperation when performed during the acute phase.

Table 487.1 Proposed RHD Definitions

Latent RDH	All cases of RHD diagnosed through echocardiographic screening, to include previously unrecognized clinical RHD and subclinical RHD.
Clinical RDH	All cases of RHD that have clinical signs or symptoms, including pathologic heart murmur* diagnosed either through echocardiographic screening or clinical evaluation. Clinical RHD is typically more advanced than subclinical RHD.
Subclinical RDH	All cases of RHD that do not have clinical signs or symptoms, including heart murmur.* Subclinical RHD is only diagnosed by echocardiography and is typically less advanced than clinical RHD.

*Detection of a pathologic heart murmur without echocardiography has been shown to be poorly sensitive and specific in echocardiographic screening studies for RHD.
RHD, Rheumatic heart disease.
Modified from Beaton A, Engelman D, Mirabel M. Echocardiographic screening for rheumatic heart disease. In: Dougherty S, Carapetis J, Zühlke, Wilson N, eds. *Acute Rheumatic Fever and Rheumatic Heart Disease.* Philadelphia: Elsevier; 2021: Table 13.1.

Mitral Stenosis

Mitral stenosis of rheumatic origin results from fibrosis of the mitral ring, commissural adhesions, and contracture of the valve leaflets, chordae, and papillary muscles over time. This is a chronic process and often takes ≥10 years for the lesion to become fully established, although the process may occasionally be accelerated. In the developed world, rheumatic mitral stenosis is seldom encountered before adolescence and is not usually recognized until adult life. Significant mitral stenosis results in increased left atrial pressure and subsequent enlargement and hypertrophy of the left atrium, pulmonary venous hypertension, increased pulmonary vascular resistance, and eventually overt pulmonary hypertension (Fig. 487.2). RV hypertrophy and right atrial dilation ensue and are followed by RV dilation, tricuspid regurgitation, and clinical signs of right-sided heart failure.

Clinical Manifestations

Generally, the correlation between symptoms and the severity of obstruction is good. Patients with mild stenosis are asymptomatic. More severe degrees of obstruction are associated with exercise intolerance and dyspnea. Critical lesions can result in orthopnea, paroxysmal nocturnal dyspnea, and overt pulmonary edema, as well as atrial arrhythmias. When pulmonary hypertension has developed, RV dilation may result in functional tricuspid insufficiency, hepatomegaly, ascites, and edema. Hemoptysis caused by rupture of bronchial or pleurohilar veins and, occasionally, pulmonary infarction may occur.

Jugular venous pressure is increased in severe disease with heart failure, tricuspid valve disease/regurgitation, or severe pulmonary hypertension. In mild disease, the heart size is normal; however, moderate cardiomegaly is typical with severe mitral stenosis. Cardiac enlargement can be massive when AF and heart failure supervene. A parasternal RV lift is palpable when PAP is high. The principal auscultatory findings are a loud first heart sound, an opening snap of the mitral valve, and a long, low-pitched, rumbling mitral diastolic murmur with presystolic accentuation at the apex. The mitral diastolic murmur may be virtually absent in patients who are in significant heart failure from the elevated LV filling pressures. A holosystolic murmur secondary to tricuspid insufficiency may be audible at the left lower sternal border. In the presence of pulmonary hypertension, the pulmonic component of S_2 is accentuated. An early diastolic murmur may

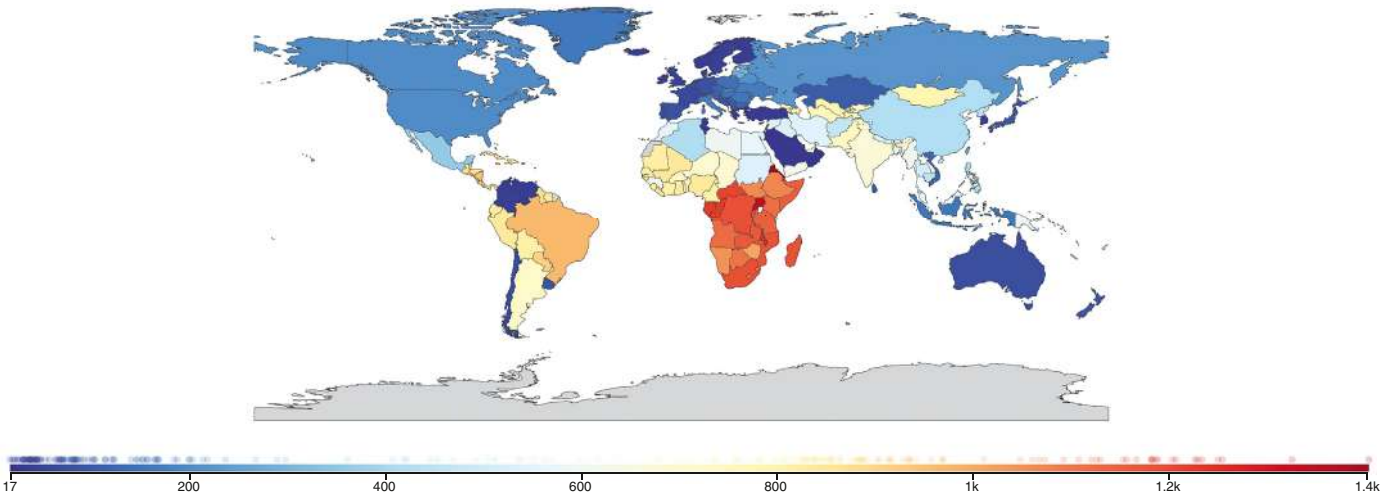

Fig. 487.1 Prevalence of rheumatic heart disease global map showing prevalence/100,000 population in 2017 by country. *(From the Institute for Health Metrics and Evaluation Global Burden of Disease 2019, Non-communicable disease data. Seattle: University of Washington IHME. https://www.healthdata.org/research-analysis/gbd.)*

be caused by associated rheumatic aortic insufficiency or pulmonary valvular insufficiency secondary to pulmonary hypertension.

ECGs and chest radiographs are normal if the stenosis is mild; as the severity increases, prominent and notched P waves and varying degrees of RV hypertrophy become evident. AF or other atrial arrhythmias are common late manifestations. Moderate to severe lesions are associated with radiographic signs of left atrial enlargement and prominence of the pulmonary artery and right-sided heart chambers; calcifications may be noted in the region of the mitral valve (see Fig. 487.2). Severe stenosis is associated with a redistribution of pulmonary blood flow so that the apices of the lung have greater perfusion (the reverse of normal). Lastly, horizontal lines in the lower lung periphery, called *Kerley B lines,* may be evident.

Echocardiography demonstrates thickening of the mitral valve and chordal apparatus, as well as restricted motion of the valve (Fig. 487.3). The typical "elbow" or "dog leg" appearance of the anterior leaflet of the mitral valve can aid in the distinction of a rheumatic valve from the various forms of congenital mitral stenosis. Left atrial dilation is common; color Doppler flow across the mitral valve shows a narrow jet with flow acceleration, and variable degrees of tricuspid insufficiency can be seen from left atrial hypertension. Doppler can estimate the transmitral pressure gradient but can underestimate the gradient if there is LV dysfunction. Estimates of the RV/PAP can be made by echocardiographic assessment of the tricuspid and pulmonary insufficiency, as well as changes in the RV size and function and the systolic septal position. Cardiac catheterization quantitates the diastolic gradient across the mitral valve well, allows for the calculation of cross-sectional valve area in older children, and assesses the degree of left atrial hypertension and PAP elevation.

Table 487.2 Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION*	PATHOLOGIC AORTIC REGURGITATION*
1. Seen in at least two views	1. Seen in at least two views
2. Jet length ≥2 cm in at least one view	2. Jet length ≥1 cm in at least one view
3. Peak velocity >3 meters/sec	3. Peak velocity >3 meters/sec
4. Pan-systolic jet in at least one envelope	4. Pan-diastolic jet in at least one envelope

*All four criteria need to be met.
Adapted from Gewitz MH, Baltimore RS, Tani LY, et al., On behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806–1818.

Table 487.3 Morphologic Findings in Echocardiogram in Rheumatic Vasculitis

ACUTE MITRAL VALVE CHANGES
Annular dilation
Chordal elongation
Chordal rupture resulting in flail leaflet with severe mitral regurgitation
Anterior (or, less commonly, posterior) leaflet tip prolapse
Beading/nodularity of leaflet tips
CHRONIC MITRAL VALVE CHANGES: NOT SEEN IN ACUTE CARDITIS
Leaflet thickening
Chordal thickening and fusion
Restricted leaflet motion
Calcification
AORTIC VALVE CHANGES IN EITHER ACUTE OR CHRONIC CARDITIS
Irregular or focal leaflet thickening
Coaptation defect
Restricted leaflet motion
Leaflet prolapse

From Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation*. 2020;142(2):e337–e357, Supplemental Table 2.

Treatment

Intervention is indicated in patients with clinical signs and hemodynamic evidence of severe obstruction, but before the onset of severe manifestations. Pharmacologic therapy (diuretics and β blockers)

Table 487.4 Recommended Durations of Secondary Prophylaxis According to International Guidelines

GUIDELINE	SECONDARY PROPHYLAXIS DURATION RECOMMENDED
American (AHA)	ARF with carditis and residual heart disease: until age 40 yr or for 10 yr after last ARF (whichever is longer); lifetime prophylaxis may be needed
	ARF with carditis but no residual heart disease: until age 21 yr or for 10 yr after last ARF (whichever is longer)
	ARF without carditis: until age 21 yr or for 5 yr after last ARF (whichever is longer)
WHO Expert Consultation Geneva (2004)	Lifelong if severe valvular disease or after valve surgery
	For 10 yr after last ARF or until age 25 yr in patients with a previous diagnosis of carditis
	For 5 yr after last ARF or until age 18 yr in patients without proven carditis

AHA, American Heart Association; ARF, acute rheumatic fever; RHD, rheumatic heart disease; WHO, World Health Organization.
Modified from Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation*. 2020;142(2):e337–e357, Table 2.

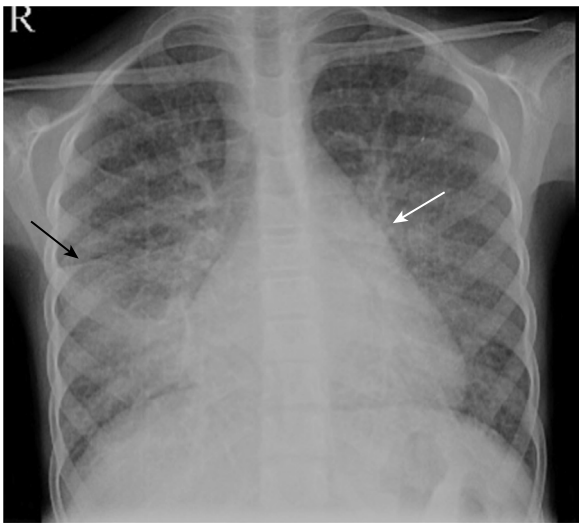

Fig. 487.2 Chest x-ray from an 8-yr-old child with advanced juvenile mitral valve stenosis. Severe pulmonary venous hypertension is shown by the prominent upper lobe vasculature, interstitial edema, and visible interlobar fissure *(black arrow)*. The left heart border is straightened, indicating enlargement of the main pulmonary artery and left atrial appendage *(white arrow)*. *(From Kumar RK, Antunes MJ, Beaton A, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. Circulation. 2020;142(2):e337–e357, Supplemental Fig. 3.)*

can be attempted but is generally used only for symptom control and much less often in children. However, it should not be considered adequate treatment in severe, symptomatic disease. Surgical valvotomy or balloon catheter mitral valvuloplasty generally yields good results (see Fig. 487.3); mitral valve replacement is avoided unless absolutely necessary. Balloon valvuloplasty is indicated for symptomatic, stenotic, pliable, noncalcified valves in patients without significant atrial arrhythmias or thrombi. Unfortunately, neither surgical nor interventional options may exist in areas of the world with high disease burden.

Aortic Insufficiency

In *acute* rheumatic aortic insufficiency, poor coaptation of the leaflets or leaflet prolapse is seen. *Chronic* rheumatic aortic insufficiency leads to sclerosis of the valve and results in distortion and retraction of the cusps. In both settings, regurgitation of blood leads to LV volume overload with dilation and hypertrophy of the left ventricle as it attempts to compensate for the excessive volume load. Concomitant mitral annular dilation accompanying LV dilation can further exacerbate mitral valve disease, specifically regurgitation. Combined mitral and aortic insufficiency in the acute phase of ARF is much more common than aortic involvement alone. However, in cases of isolated significant aortic insufficiency, RHD should not be discounted, even given the rare nature of this finding.

Clinical Manifestations

Symptoms are unusual except in severe aortic insufficiency or in the presence of significant concomitant mitral valve involvement or myocardial dysfunction. The large stroke volume and forceful LV contractions may result in palpitations. Sweating and heat intolerance are related to excessive vasodilation. Dyspnea on exertion can progress to orthopnea and pulmonary edema; angina may be precipitated by heavy exercise. Nocturnal attacks with sweating, tachycardia, chest pain, and hypertension may occur.

The pulse pressure is wide with bounding peripheral pulses (**water hammer** or **Corrigan pulse**). Systolic blood pressure is elevated, and diastolic pressure is lowered. In severe aortic insufficiency, the heart is enlarged, with an LV apical heave. A diastolic thrill may be present. The typical murmur begins immediately with S_2 and continues until late in diastole. The murmur is heard over the upper left and mid-left sternal border with radiation to the apex and upper right sternal border. Characteristically, it has a high-pitched blowing quality and is easily audible in full expiration with the diaphragm of the stethoscope placed firmly on the chest and the patient leaning forward. An aortic systolic ejection murmur is frequently heard because of the increased stroke volume. An apical presystolic murmur **(Austin Flint murmur)** resembling that of mitral stenosis is sometimes heard and is caused by the large regurgitant aortic flow in diastole preventing the mitral valve from opening fully.

Chest radiographs demonstrate enlargement of the left ventricle and aorta. The ECG may be normal, but in advanced cases it reveals signs of LV hypertrophy with a strain pattern and prominent P waves. Echocardiography shows a dilated left ventricle and diastolic mitral valve flutter or oscillations caused by aortic regurgitant flow hitting the valve leaflets. The aortic valve may demonstrate irregular or focal thickening, decreased systolic excursion, a coaptation defect, and leaflet prolapse. Doppler evaluation demonstrates the degree of aortic insufficiency. Cardiac magnetic resonance imaging/angiography (cMRI/MRA) can be useful in quantitating regurgitant volume and in assessing LV size and systolic function. Cardiac catheterization is generally only necessary when echocardiographic or axial imaging data are equivocal.

Prognosis and Treatment

Mild and moderate degrees of aortic insufficiency are well tolerated. Unlike mitral insufficiency, aortic insufficiency does not generally regress. Patients with combined lesions during the episode of ARF may have only aortic involvement 1-2 years later. Treatment consists of ACE inhibitors or ARBs and prophylaxis against ARF recurrence. Surgical intervention, which is typically aortic valve repair but occasionally can involve aortic valve prosthetic (biologic or mechanical) replacement, should be done well in advance of the onset of heart failure, pulmonary edema, and angina or when signs of decreasing myocardial performance become evident, as manifested by increasing LV dimensions and decreasing systolic function on echocardiography. Surgery is considered when early symptoms are present, significant ST-T wave changes are seen on the ECG, or evidence of decreasing LV ejection fraction is noted.

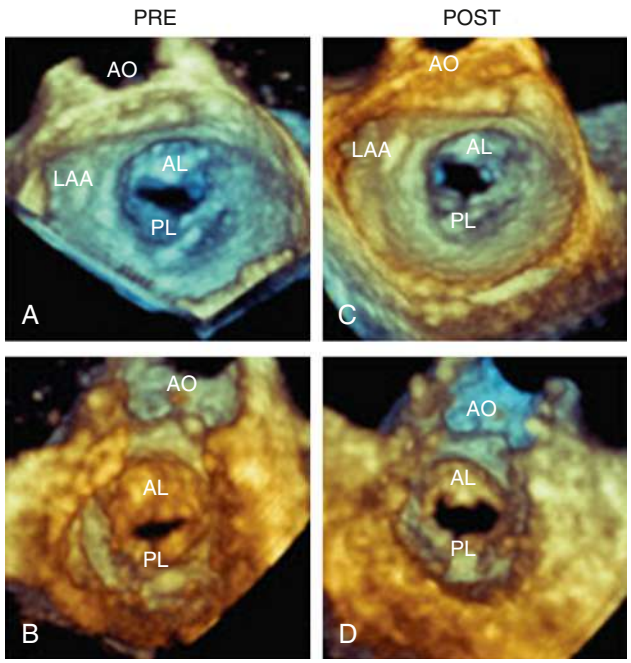

Fig. 487.3 Balloon mitral valvotomy. Real-time three-dimensional transesophageal echocardiographic images obtained before, during, and after balloon mitral valvotomy in a patient with mitral stenosis. A and B illustrate the stenotic mitral orifice as seen from the left atrium (A) and from the left ventricle (B) immediately prior to the procedure. C and D, obtained immediately after the procedure, show the commissure splitting and the larger mitral valve orifice. AL, anterior leaflet; AO, aorta; LAA, left atrial appendix; PL, posterior leaflet. *(From Salcedo EE, Carroll JD. Imaging guidance of transcatheter valve procedures. In Otto CM, Bonow RO (eds). Valvular Heart Disease: A Companion to Braunwald's Heart Disease. Philadelphia: Elsevier, 2013. Fig 16.11.)*

Tricuspid Valve Disease

Primary tricuspid valve involvement is rare during both the acute and chronic stages of rheumatic fever. Tricuspid insufficiency is more common secondary to RV dilation, resulting from significant left-sided cardiac lesions. The clinical signs of tricuspid insufficiency include prominent pulsations of the jugular veins, systolic pulsations of the liver, and a blowing holosystolic murmur at the lower left sternal border that increases in intensity during inspiration. Concomitant signs of mitral or aortic valve disease, with or without AF, are common. In these cases, signs of tricuspid insufficiency often decrease or even disappear when heart failure produced by the left-sided valvular lesions is successfully treated. Tricuspid valvuloplasty may be required in very rare cases.

Pulmonary Valve Disease

Pulmonary insufficiency secondary to ARF is rare and usually occurs on a functional basis secondary to pulmonary hypertension and is a late finding with severe mitral stenosis. The murmur **(Graham Steell murmur)** is similar to that of aortic insufficiency, but peripheral arterial signs (bounding pulses) are absent. The correct diagnosis is confirmed by two-dimensional echocardiography and Doppler studies demonstrating nonphysiologic pulmonary insufficiency, evidence of pulmonary hypertension, and the presence of mitral valve disease. Surgical intervention on the pulmonary valve is highly unusual.

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Section 6

Diseases of the Myocardium and Pericardium

Chapter 488

Diseases of the Myocardium

John J. Parent and Stephanie M. Ware

The heterogeneous heart muscle diseases associated with structural remodeling and abnormalities of cardiac function **(cardiomyopathy)** are important causes of morbidity and mortality in the pediatric population. Several classification schemes have been formulated in an effort to provide logical, useful, and scientifically based etiologies for the cardiomyopathies. Insight into the molecular genetic basis of cardiomyopathies has increased exponentially, and etiologic classification schemes continue to evolve (Table 488.1).

Table 488.2 classifies the cardiomyopathies based on their anatomic (ventricular morphology) and functional pathophysiology. **Dilated cardiomyopathy**, the most common form of cardiomyopathy, is characterized predominantly by left ventricular (LV) dilation and decreased LV systolic function (Fig. 488.1). **Hypertrophic cardiomyopathy** demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities with fibrosis of varying degrees (Table 488.3 and Figs. 488.2 and 488.3). **Restrictive cardiomyopathy** is characterized by near-normal ventricular chamber size and wall thickness with preserved systolic function but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement (Fig. 488.4). **Arrhythmogenic right ventricular (RV) cardiomyopathy** is characterized by fibrofatty infiltration and replacement of the normal RV myocardium and occasionally the left ventricle, leading to RV (and LV) systolic and diastolic dysfunction and arrhythmias. **Left ventricular noncompaction** is characterized by a hypertrabeculated LV apex and lateral wall, with a heterogeneous group of associated phenotypes (most often a dilated phenotype with LV dilation and dysfunction). Cardiomyopathies may be primary or associated with other organ involvement (Tables 488.4-488.6).

488.1 Dilated Cardiomyopathy

John J. Parent and Stephanie M. Ware

Dilated cardiomyopathy **(DCM)**, the most common form of cardiomyopathy in children, is the cause of significant morbidity and mortality and a common indication for cardiac transplantation. The etiologies are diverse. Unlike adult patients with DCM, ischemic etiologies are rare in children, although these include anomalous origin of the left coronary artery from the pulmonary artery, premature coronary atherosclerosis (homozygous familial hypercholesterolemia, rare genetic syndromic diseases such as progeria), and coronary inflammatory diseases such as Kawasaki disease. It is estimated that up to 50% of cases are **genetic** (usually autosomal dominant; some are autosomal recessive or X-linked), including some with metabolic causes (see Tables 488.1 and 488.2). Although the most common etiology of DCM remains **idiopathic**, it is likely that undiagnosed familial/genetic conditions and myocarditis predominate. The annual incidence of DCM in children younger than 18 years is 0.57 cases per 100,000 per year. The incidence is higher in males, Blacks, and infants <1 year old.

PATHOGENESIS

The pathogenesis of the ventricular dilation and altered contractility seen in DCM varies depending on the underlying etiology; systolic dysfunction and myocyte injury are common. Genetic abnormalities of several components of the cardiac muscle, including sarcomere proteins, the cytoskeleton, and the proteins that bridge the contractile apparatus to the cytoskeleton, have been identified in autosomal dominant and X-linked inherited disorders. DCM can occur after viral myocarditis. Although the primary pathogenesis varies from direct myocardial injury to viral-induced inflammatory injury, the resulting myocardial damage, ventricular enlargement, and poor function likely occur by a final common pathway similar to that in genetic disorders.

In 20–50% of cases, the DCM is familial, with autosomal dominant inheritance most common (see Table 488.3). **Duchenne and Becker muscular dystrophies** are X-linked cardiomyopathies that account for 5–10% of DCM cases (see Chapter 649.1). These dystrophinopathies result in an abnormal sarcomere-cytoskeleton connection, causing impaired myocardial force generation, myocyte damage/scarring, chamber enlargement, and altered function (see Table 488.6). Female carriers of dystrophinopathies may also manifest DCM.

Mitochondrial myopathies, as with the muscular dystrophies, may present clinically with a predominance of extracardiac findings, although in some children cardiomyopathy may be the first symptom. These are inherited in a recessive or mitochondrial pattern (see Tables 488.4 and 488.5). Disorders of **fatty acid oxidation** present with systemic derangements of metabolism (hypoketotic hypoglycemia, acidosis, and hepatic dysfunction), some with peripheral myopathy and neuropathy, and others with sudden death or life-threatening cardiac arrhythmias.

Anthracycline cardiotoxicity (doxorubicin [Adriamycin]) on rare occasion causes acute inflammatory myocardial injury, but more classically results in DCM and occurs in up to 30% of patients given a cumulative dose of doxorubicin exceeding 550 mg/m^2. The risk of toxicity appears to be exacerbated by concomitant radiation therapy.

CLINICAL MANIFESTATIONS

Although more prevalent in patients <1 year of age, all age-groups may be affected. Clinical manifestations of DCM are typically those of heart failure but can also include palpitations, syncope, and sudden death. Irritability or lethargy can be accompanied by additional nonspecific complaints of failure to thrive, nausea, vomiting, or abdominal pain. Respiratory symptoms (tachypnea, wheezing, cough, orthopnea, or dyspnea on exertion) are often present. Infrequently, patients may present acutely with pallor, altered mentation, hypotension, and shock. Patients can be tachycardic with narrow pulse pressure and may have hepatic enlargement and rales or wheezing. The precordial cardiac impulse is increased, and the heart may be enlarged to palpation or percussion. Auscultation may reveal a gallop rhythm in addition to tachycardia, and occasionally murmurs of mitral or, less often, tricuspid insufficiency may be present. The presence of hypoglycemia, acidosis, hypotonia, or signs of liver dysfunction suggests an inborn error of metabolism. Neurologic or skeletal muscle deficits are associated with mitochondrial disorders or muscular dystrophies (see Tables 488.4-488.6).

LABORATORY FINDINGS

Electrocardiographic screening reveals atrial or ventricular hypertrophy, nonspecific T-wave abnormalities, and occasionally, atrial or ventricular arrhythmias. The chest radiograph may demonstrate cardiomegaly and pulmonary vascular prominence or pleural effusions. The echocardiogram is often diagnostic, demonstrating the characteristic findings of LV enlargement, decreased ventricular contractility, and occasionally a globular (remodeled) LV contour (see Fig. 488.1).

Table 488.1 Classification of the Cardiomyopathies by Phenome and Genome

	PHENOTYPE				GENOME	
TYPE	**MORPHOLOGY**	**PHYSIOLOGY**	**PATHOLOGY**	**SYSTEMIC CONDITIONS, CLINICAL FEATURES, RISK FACTORS**	**NONSYNDROMIC, USUALLY SINGLE GENE**	**SYNDROMIC**
Dilated (DCM)	Dilation of LV and RV with minimal or no wall thickening	Reduced contractility is the primary defect; variable degree of diastolic dysfunction	Myocyte hypertrophy; scattered fibrosis	Hypertension, alcohol, thyrotoxicosis, myxedema, persistent tachycardia, toxins (e.g., chemotherapy, especially anthracyclines), radiation	Diverse gene ontology with >50 genes implicated	Diverse array of associated conditions, especially muscular dystrophies: Emery-Dreifuss, limb-girdle, Duchenne/Becker; Laing distal myopathy; Barth syndrome; Kearns-Sayre syndrome; other mitochondrial disorders; fatty acid oxidation disorders; Alstrom syndrome, others
Restrictive (RCM)	Usually normal chamber sizes; minimal wall thickening	Contractility normal or near-normal with a marked increase in end-diastolic filling pressure	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others	Endomyocardial fibrosis, amyloid, sarcoid, scleroderma, Churg-Strauss syndrome, cystinosis, lymphoma, pseudoxanthoma elasticum, hypereosinophilic syndrome, carcinoid	If not associated with systemic genetic disease, genetic cause usually from sarcomeric pathogenic gene variants	Gaucher disease, hemochromatosis, Fabry disease, familial amyloidosis, mucopolysaccharidoses, Noonan syndrome
Hypertrophic (HCM)	Usually normal or reduced internal chamber dimension; wall thickening pronounced, especially septal hypertrophy	Systolic function increased or normal	Myocyte hypertrophy, classically with disarray	Severe hypertension can confound clinical, morphologic diagnosis	Pathogenic variants of genes encoding sarcomeric proteins	Noonan syndrome, Noonan syndrome with multiple lentigines, Danon syndrome, Fabry disease, Wolff-Parkinson-White syndrome, Friedreich ataxia, MERRF, MELAS, other mitochondrial disorders, fatty acid oxidation disorders
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Scattered fibrofatty infiltration, classically of RV but also of LV; dilation of RV or LV, or both, is common but not universal	Ventricular arrhythmias (VT, VF) early or late, reduced contractility with progressive disease; can mimic DCM	Islands of fatty replacement; fibrosis	Palmoplantar keratoderma, wooly hair in Naxos syndrome	Pathogenic variants of genes encoding proteins of desmosome	Naxos syndrome
Left ventricular noncompaction (LVNC)	Ratio of noncompacted to compacted myocardium increased with normal LV or RV or any other phenotype	Normal to reduced systolic function	Myocardium normal and ranging to findings consistent with other coexisting cardiomyopathies	Phenotype observed in setting of other types of cardiomyopathy	Various cardiomyopathy genes associated, but uncertain whether genetic cause or developmental defect during organogenesis	

Continued

Table 488.1 Classification of the Cardiomyopathies by Phenome and Genome—cont'd

	PHENOTYPE				GENOME	
TYPE	**MORPHOLOGY**	**PHYSIOLOGY**	**PATHOLOGY**	**SYSTEMIC CONDITIONS, CLINICAL FEATURES, RISK FACTORS**	**NONSYNDROMIC, USUALLY SINGLE GENE**	**SYNDROMIC**
Infiltrative	Usually thickened walls; occasional dilation	Restrictive physiology; systolic function usually mildly reduced	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others		See RCM earlier	See RCM earlier
Inflammatory	Normal or dilated without hypertrophy	Reduced systolic function	Inflammatory infiltrates	Hypereosinophilic syndrome, acute myocarditis		
Ischemic	Normal or dilated without hypertrophy	Reduced systolic function	Areas of infarcted myocardium	Hypercholesterolemia, hypertension, diabetes, cigarette smoking, family history	Familial hypercholesterolemia; other heritable lipid disorders	Familial hypercholesterolemia
Infectious	Normal or dilated without hypertrophy	Reduced systolic function	Specific to infection	Viral (especially acute myocarditis); protozoal (e.g., Chagas disease); bacterial, direct infection (e.g., Lyme disease), or from acute cellular toxicity as result of systemic toxins (e.g., *Streptococcus*, gram-negative, others)	Genetic predisposition to infection and/or variable response to infective agent	

LV, Left ventricle; MELAS, mitochondrial encephalopathy, lactic acidosis, and strokelike symptoms; MERRF, myoclonic epilepsy associated with ragged-red fibers; RV, right ventricle; VF, ventricular fibrillation; VT, ventricular tachycardia.
From Falk RH, Hershberger RE. The dilated, restrictive, and infiltrative cardiomyopathies. In: Zipes DP, Libby P, Bonow RO, et al., eds. *Braunwald's Heart Disease*, 11th ed. Philadelphia: Elsevier; 2019: Table 77.1.

Table 488.2 Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular diseases	Muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, Emery-Dreifuss, congenital muscular dystrophy), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD, LCHAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia), Danon disease (DCM more common in females)
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alström syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	Atrial tachycardias (intractable reentrant supraventricular tachycardia [AVRT, AVNRT], multifocal atrial tachycardia, permanent junctional reciprocating tachycardia), ventricular tachycardia
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, variants in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease); fatty acid oxidation disorders
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, and Beckwith-Wiedemann syndromes
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic RCM
Secondary	Rare in children; radiation therapy of thorax, amyloidosis, sarcoidosis, hemochromatosis, β-thalassemia
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic variants in cardiomyocyte structural apparatus	Familial or sporadic ARVC
Left Ventricular Noncompaction	
Genetic variants in cardiomyocyte structural apparatus	LVNC phenotype associated with HCM or DCM
Other	X-linked (Barth syndrome), autosomal recessive, mitochondrial inheritance, 1p36 deletion syndrome, and other chromosome abnormalities or genomic disorders; associated with congenital heart defects
SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 488.7)	**Viral:** parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV, SARS-CoV-2 (COVID-19), opportunistic infections **Rickettsial:** psittacosis, *Coxiella,* Rocky Mountain spotted fever, typhus **Bacterial:** diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis **Parasitic:** Chagas disease, toxoplasmosis, *Loa loa, Toxocara canis,* schistosomiasis, cysticercosis, echinococcus, trichinosis **Fungal:** histoplasmosis, coccidioidomycosis, actinomycosis
Systemic inflammatory disease	SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease, multisystem inflammatory syndrome in children (COVID-19)
Nutritional deficiency	Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)
Drugs, toxins	Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh), immune checkpoint inhibitors
Coronary artery disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from pulmonary artery, other congenital coronary anomalies (anomalous right coronary artery, coronary ostial stenosis), familial hypercholesterolemia
Hematology-oncology	Anemia, sickle cell disease, leukemia
Endocrine-neuroendocrine	Hyperthyroidism, carcinoid tumor, pheochromocytoma, adrenal crisis
Stress (takotsubo) cardiomyopathy	Endocrine (see earlier) Neurologic (stroke, bleed) Induction of anesthesia Fright Medications/drugs (sympathomimetic agents, venlafaxine)

CPTI/CPTII, Carnitine palmitoyltransferase 1/2; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very-long-chain acyl-coenzyme A dehydrogenase.

RV enlargement and depressed function are occasionally noted. Echo Doppler studies can reveal evidence of pulmonary hypertension, mitral regurgitation, or other structural cardiac or coronary abnormalities. Cardiac MRI is useful for patients with suboptimal imaging echocardiographic windows or in patients with concern of acute myocarditis where, in contrast to echocardiography, recognition of inflammation of the myocardium is possible.

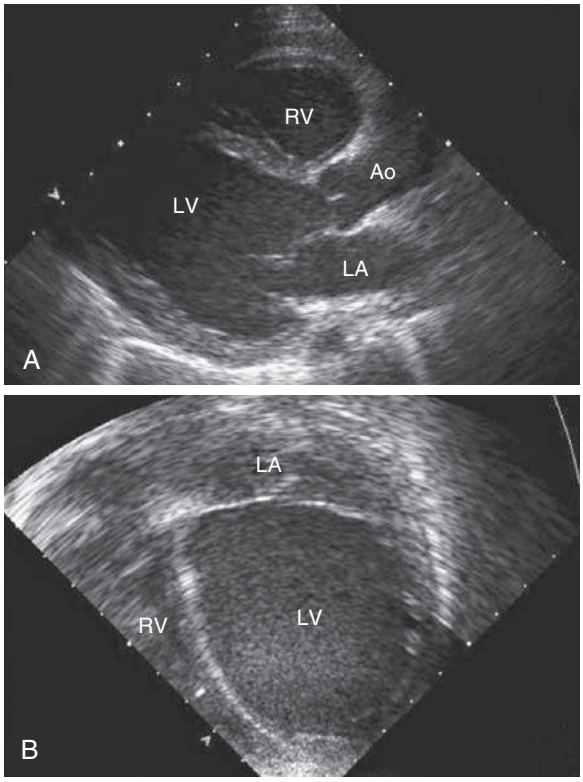

Fig. 488.1 Echocardiogram of a patient with dilated cardiomyopathy. **A,** Parasternal long-axis view showing the enlarged left ventricle. **B,** Apical four-chamber view showing the large left ventricle compressing the right ventricle. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Additional testing may include complete blood count, renal and liver function tests, creatine phosphokinase (CPK), cardiac troponin I, lactate, brain natriuretic peptide (BNP) and pro-BNP, plasma amino acids, urine organic acids, and an acylcarnitine profile. Additional genetic testing is typically indicated, and enzymatic testing may be useful (see Table 488.3). Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute DCM. Biopsy samples can be examined histologically for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and evidence of infection. It is considered standard of care to screen first-degree family members using echocardiography and electrocardiogram (ECG) in idiopathic and familial cases of DCM.

PROGNOSIS AND MANAGEMENT

The 1- and 5-year freedom from death or transplantation in patients diagnosed with DCM is 60–70% and 50–60%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation include older age, heart failure, lower LV fractional shortening *z* score, and underlying etiology. DCM is the most common cause for cardiac transplantation in pediatric and adult studies.

The therapeutic approach to patients with DCM includes a careful assessment to uncover possible treatable etiologies, screening of family members, and rigorous pharmacologic therapy. **Medications** aimed at reverse remodeling (improving ventricular size and function) include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) plus β-adrenergic blockade with carvedilol or metoprolol. The combination medication valsartan/sacubitril, which is an ARB/neprilysin inhibitor, respectively, that is FDA approved for patients 1 year of age and older, has been readily used in this setting in pediatrics in lieu of either an ACE or ARBs alone (see Chapter 491). Each of these medications have proved independently and in combination to improve survival and symptoms and reduce hospital admissions in adults with DCM. Additionally, furosemide may be used to reduce symptoms of pulmonary or systemic venous congestion. Digoxin therapy can also be considered in some patients. Implantable cardiac defibrillators may be considered for certain select patients with a high risk of sudden cardiac arrest. **Pacemakers**, including dual-chamber and biventricular pacing therapy, can improve patients with

Table 488.3 Cardiomyopathies

	DCM	HCM	RCM	LVNC	ARVC
Prevalence	50/100,000	1/500	Unknown	Unknown	1/2,000
Causes	Sarcomeric/ cytoskeletal/ desmosomal gene variant, neuromuscular disease, inborn error of metabolism, mitochondrial disease, genetic syndrome, infection	Sarcomeric/ cytoskeletal/ desmosomal gene variant, genetic syndrome, inborn error of metabolism/ mitochondrial disease	Sarcomeric gene variant, neuromuscular disease, genetic syndrome, storage or infiltrative disease	Sarcomeric-cytoskeletal-desmosomal gene mutation, neuromuscular disease, inborn error of metabolism, mitochondrial disease, genetic syndrome	Desmosomal gene variants
Inheritance	30–50% AD, AR, X-L, Mt	50% AD, Mt	AD, up to 50%	AD, X-L, Mt, % unknown	30–50% AD, rare AR (Naxos disease; Carvajal syndrome)
Sudden death	Yes	Yes	Yes	Yes	Yes
Arrhythmias	Atrial, ventricular, and conduction disturbances	Atrial and ventricular	Atrial fibrillation	Atrial, ventricular, and conduction disturbances	Ventricular and conduction disturbances
Ventricular function	Systolic and diastolic dysfunction	Diastolic dysfunction Dynamic systolic outflow obstruction	Diastolic dysfunction Normal systolic function	Systolic or diastolic dysfunction	Normal-reduced systolic and diastolic function

ACE, Angiotensin-converting enzyme; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVNC, left ventricular noncompaction; Mt, mitochondrial inheritance; RCM, restrictive cardiomyopathy; X-L, X-linked inheritance.

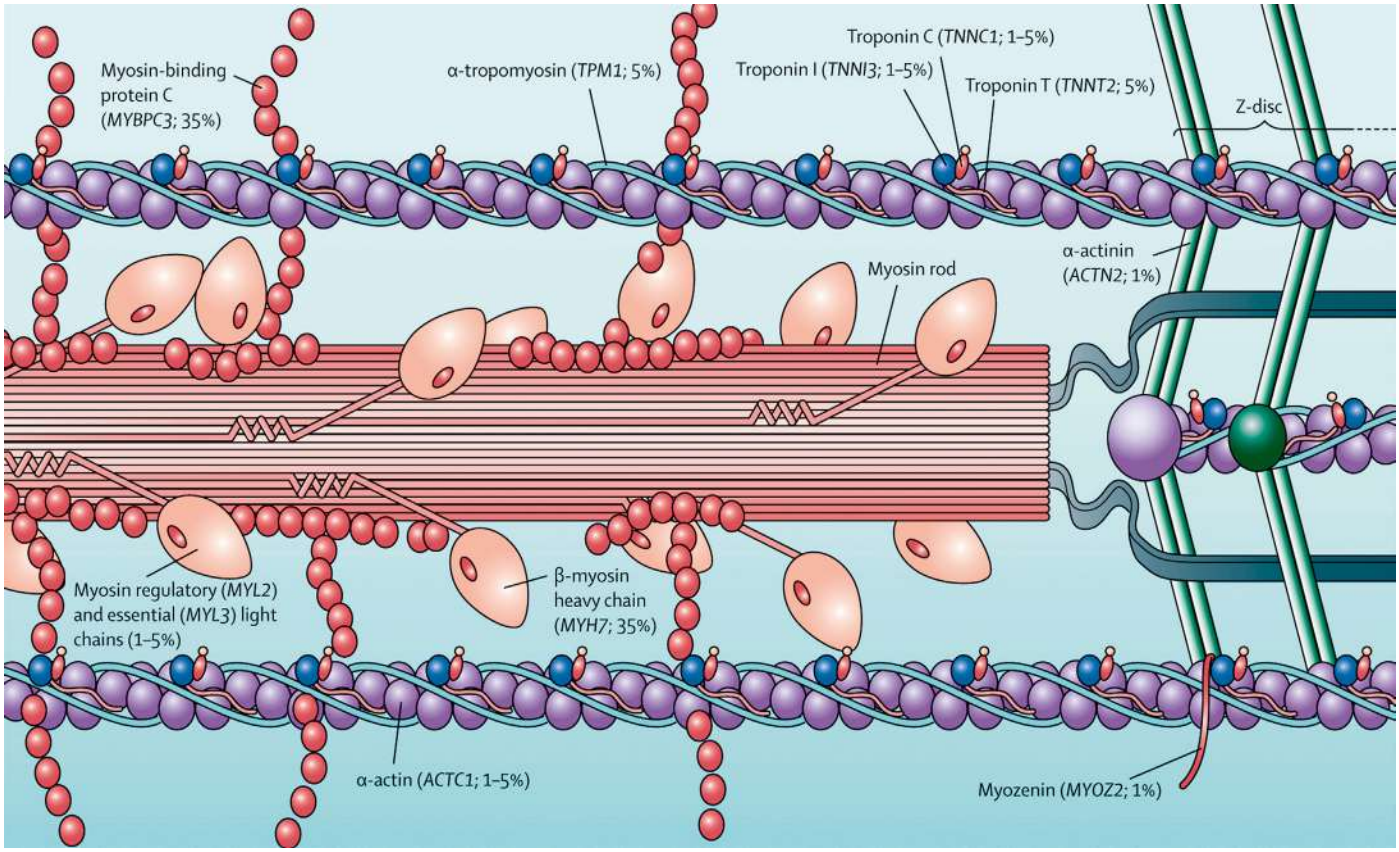

Fig. 488.2 Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy. Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses. *(From Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381:242–252, Fig 1.)*

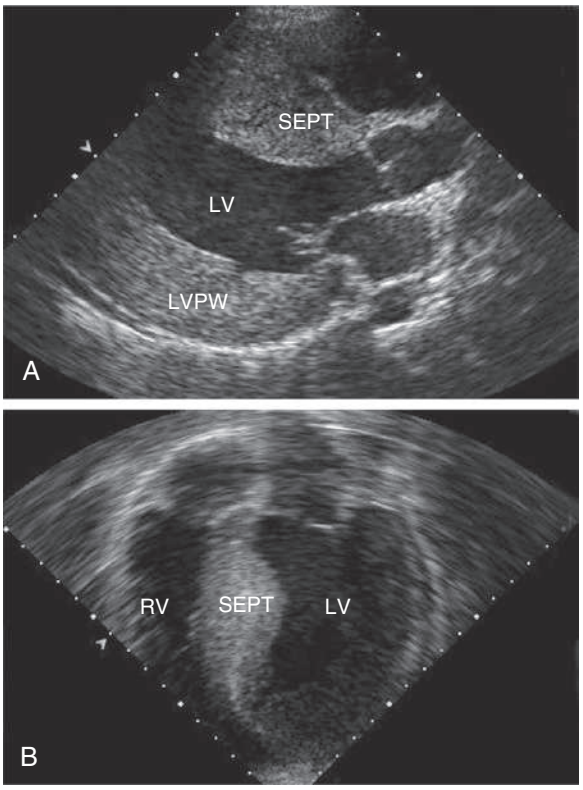

Fig. 488.3 Echocardiograms demonstrating hypertrophic cardiomyopathy. A, Parasternal long-axis view of a patient with severe concentric left ventricular hypertrophy. B, Four-chamber view of a patient with asymmetric septal hypertrophy. LV, Left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; SEPT, septum.

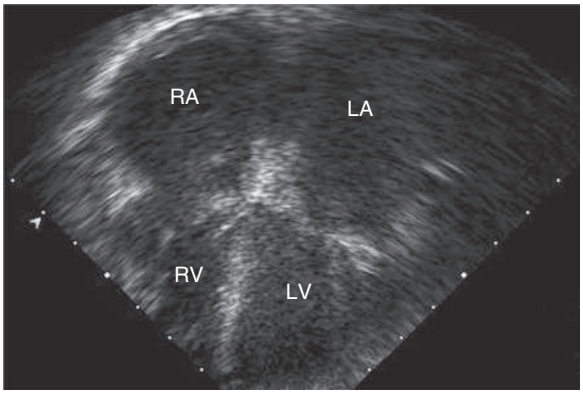

Fig. 488.4 Echocardiogram of a patient with restrictive cardiomyopathy. Apical four-chamber view shows the greatly enlarged right and left atria compared to the normal-size left and right ventricular chambers. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 488.4 Nuclear DNA Abnormalities Associated with Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
ISOLATED COMPLEX DEFICIENCIES			
Complex I deficiency	Multiple complex I subunit genes, *ACAD9, FOXRED1*	HCM, DCM, LVNC, WPW	Leigh syndrome, FILA, MELAS, leukoencephalopathy, seizures, hypotonia, pigmentary retinopathy, optic atrophy, hearing loss, liver dysfunction
Complex II deficiency	*SDHA, SDHD*	HCM, DCM, LVNC, AF, heart block	Leukoencephalopathy, cerebellar atrophy, seizures, spasticity, myopathy, liver dysfunction, kidney dysfunction
Complex III deficiency	*BCS1L*	HCM	Developmental delay, psychosis, hearing loss
Complex IV deficiency	*SCO2, SURF1, C2orf64, Cl2orf62, COX6B1*	HCM, DCM	Leigh syndrome, encephalopathy, ataxia, liver dysfunction, kidney dysfunction
MITOCHONDRIAL TRANSLATION DEFECTS			
GTP-binding protein-3 deficiency	*GTPBP3*	HCM, DCM, heart block, WPW	Leigh syndrome, encephalopathy
Mitochondrial translational activator protein deficiency	*MTOI*	HCM, heart block	Encephalopathy, hypotonia
Alanyl-tRNA synthetase deficiency	*AARS2*	HCM	Leukoencephalopathy, myopathy
Tyrosyl-tRNA synthetase deficiency	*YARS2*	HCM	MLASA syndrome
tRNA methyltransferase-*5* deficiency	*TRMTS*	HCM	Developmental delay, hypotonia, peripheral neuropathy, renal tubulopathy
RNA processing defect	*ELAC2*	HCM, PSVE	Microcephaly, growth deficiency, hearing loss
Mitochondrial ribosomal subunit deficiencies	*MRPS22, MRPl3, MRPL44*	HCM, WPW	Leukoencephalopathy, seizures, liver dysfunction, renal tubulopathy
mtDNA DEPLETION SYNDROMES			
MNGIE	*TYMP*	Mild or asymptomatic HCM	Leukoencephalopathy, severe gastrointestinal dysmotility, ophthalmoplegia, hearing loss, peripheral neuropathy
F-box protein deficiency	*FBXL4*	Cardiomyopathy, unspecified	Encephalopathy, brain atrophy
Coenzyme Q_{10} biosynthesis defects	*COQ2, COQ4, COQ9*	HCM	Leigh syndrome, encephalomyopathy, retinitis pigmentosa, hearing loss, liver dysfunction, renal tubulopathy
3-METHYLGLUTACONIC ACIDURIAS			
Barth syndrome	*TAZ*	HCM, DCM, LVNC, EFE, VT, LQTS	Myopathy, short stature, neutropenia
Dilated cardiomyopathy and ataxia syndrome	*DNAJC19*	DCM, LVNC	Ataxia, optic ataxia, short stature, testicular abnormalities, liver disease
Complex V deficiency	*TMEM70*	HCM	Cataracts, leukodystrophy, ataxia, myopathy, short stature
Sengers syndrome	*AGK*	HCM	Cataracts, myopathy, exercise intolerance, short stature

*Examples of conditions that are associated with heart disease and feature abnormal nDNA are shown, along with the causative molecular defects and clinical findings. The genetic defects noted here are provided as major contributors to the various mitochondrial conditions but are not a comprehensive compilation.

AF, Atrial fibrillation; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; FILA, fatal infantile lactic acidosis; GTP, guanosine triphosphate; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MLASA, myopathy, lactic acidosis, sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalopathy; nDNA, nuclear DNA; PSVE, paroxysmal supraventricular extrasystoles; LVNC, left ventricular noncompaction; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

From Enns GM. Pediatric mitochondrial diseases and the heart. *Curr Opin Pediatr*. 2017;29:541–551, Table 2.

certain underlying electrical derangements. In patients presenting with extreme degrees of heart failure or circulatory collapse, intensive care measures are often required, including intravenous inotropes and diuretics, mechanic ventilatory support, and on occasion, mechanical circulatory support, which may include a ventricular assist device (VAD), total artificial heart, extracorporeal membrane oxygenation (ECMO), and ultimately cardiac transplantation. In patients with DCM and atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be instituted.

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Table 488.5 Mitochondrial DNA Abnormalities Associated with Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
Kearns-Sayre syndrome	mtDNA deletion	HCM, DCM, heart block, PMVT	Progressive external ophthalmoplegia, pigmentary retinopathy, cerebellar ataxia, hearing loss, increased CSF protein, diabetes mellitus, renal tubulopathy
MELAS	$tRNA^{Lou}$ point variant	HCM, DCM, LVNC, RCM, heart block, WPW	Encephalopathy, seizures, strokelike episodes, headaches, hearing loss, myopathy
MERRF	$tRNA^{Lys}$ point variant	HCM, DCM, HiCM, WPW	Myoclonus, seizures, ataxia, optic atrophy, hearing loss, short stature
Complex I deficiency	Multiple complex I subunit genes	HCM, DCM	Leigh syndrome, leukoencephalopathy, seizures, optic atrophy
Complex III deficiency	*MTCYB*	HCM, DCM, HiCM	Exercise intolerance, myopathy, seizures, optic atrophy, short stature
Complex IV deficiency	*MT-CO1, MT-CO2, MT-CO3*	HCM, DCM, HiCM	Encephalopathy, seizures, pigmentary retinopathy, hearing loss, myopathy, liver dysfunction
Complex V deficiency	*MT-ATP6, MT-ATP8*	HCM	Ataxia, peripheral neuropathy

*Relatively common conditions that are associated with heart disease and feature abnormal mtDNA are shown, along with the most common molecular defects and clinical findings. Although the most common molecular defects are indicated in the table, in most cases, multiple genetic abnormalities can cause similar clinical presentations.

CSF, Cerebrospinal fluid; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HiCM, histiocytoid cardiomyopathy; LVNC, left ventricular noncompaction; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonic epilepsy with ragged red fibers; mtDNA, mitochondrial DNA; PMVT, polymorphic ventricular tachycardia; RCM, restrictive cardiomyopathy; WPW, Wolff-Parkinson-White syndrome.

From Enns GM. Pediatric mitochondrial diseases and the heart. *Curr Opin Pediatr.* 2017;29:541–551. Table 3.

Table 488.6 Gene Variants and Cardiac Manifestations of Neuromuscular Disorders

DISORDER	GENE VARIANT	CARDIOMYOPATHY	ECG	ARRHYTHMIA
Duchenne muscular dystrophy (DMD)	Dystrophin	Dilated	Short PR interval, prolonged QT interval, increased QT:PT ratio, right ventricular hypertrophy, deep Q waves II, III, aVF, V_5, V_6	Increased baseline HR, decreased rate variability, premature ventricular beats (58% of patients by 24 yr of age)
DMD—female carrier	Dystrophin	Dilated	None	Uncommon
Becker muscular dystrophy	Dystrophin	Dilated	Conduction system disease	Similar to DMD
Emery-Dreifuss autosomal dominant or proximal dominant limb-girdle muscular dystrophy IB	Lamin A/C	Dilated	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill; ventricular dysrhythmias
Limb-girdle muscular dystrophy	α, β, γ, δ sarcoglycans	Dilated	Incomplete right bundle branch block, tall R waves in V_1 and V_2, left anterior hemiblock	Uncommon
Congenital muscular dystrophy	Laminin α_2	Dilated	None	None
Limb-girdle muscular dystrophy 21	Fukutin	Dilated	AV node and bundle branch block; age at onset: late teens and early 20s	Atrial arrhythmias and/or ventricular arrhythmias
Emery-Dreifuss X-linked	Emerin	Rare	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill
Friedreich ataxia	Frataxin	Hypertrophic	T-wave inversion, left axis deviation, repolarization abnormalities	Ventricular arrhythmias
Myotonic dystrophy type 1, infantile	Myotonic dystrophy protein kinase gene	Hypertrophic	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block
Myotonic dystrophy type 1	Myotonic dystrophy protein kinase gene	LVNC	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block

AV, Atrioventricular; HR, heart rate; LVNC, left ventricular noncompaction.

From Hsu DT. Cardiac manifestations of neuromuscular disorders in children. *Pediatr Respir Rev.* 2010;11:35–38, Table 1.

488.2 Hypertrophic Cardiomyopathy

John J. Parent and Stephanie M. Ware

Hypertrophic cardiomyopathy **(HCM)** is a heterogeneous, relatively common, and potentially life-threatening form of cardiomyopathy. The causes of HCM include inborn errors of metabolism, neuromuscular disorders, syndromic conditions, and genetic abnormalities of the structural components of the cardiomyocyte (see Tables 488.1 and 488.2). Both the age of onset and the associated features are helpful in identifying the underlying etiology.

HCM is a genetic disorder and frequently occurs because of pathogenic variants in sarcomere or cytoskeletal components of the cardiomyocyte (see Fig. 488.2). Pathogenic variants of the genes encoding cardiac β-myosin heavy-chain *(MYH7)* and myosin-binding protein C *(MYBPC3)* are the most common (see Table 488.3). Pathogenic variants are inherited in an autosomal dominant pattern with a high penetrance but variable expressivity. Additional genetic causes for HCM include nonsarcomeric protein pathogenic variants, such as the γ_2-regulatory subunit of adenosine monophosphate–activated protein kinase *(PRKAG2)* and the lysosome-associated membrane protein 2α-galactosidase (**Danon disease**, a form of glycogen storage disease). Syndromic conditions, such as **Noonan syndrome**, may present with HCM at birth, and recognition of extracardiac manifestations is important in making the diagnosis. Medical therapy directed at the Ras signaling pathway is in the initial phases of use in patients with Noonan syndrome and related RASopathies.

Glycogen storage disorders such as **Pompe disease** often present in infancy with a heart murmur, abnormal ECG, systemic signs and symptoms, and occasionally heart failure. Many states have Pompe testing on the newborn screening, facilitating early diagnosis and therapy, which has improved the prognosis. The characteristic ECG in Pompe disease demonstrates prominent P waves, a *short* P-R interval, and massive QRS voltages. The echocardiogram confirms severe, often concentric, LV hypertrophy.

PATHOGENESIS

HCM is characterized by the presence of increased LV wall thickness in the absence of structural heart disease or hypertension. Often the interventricular septum is disproportionately involved, leading to the previous designation of *idiopathic hypertrophic subaortic stenosis* or the current term of **asymmetric septal hypertrophy**. In the presence of a resting or provocable outflow tract gradient, the term **hypertrophic obstructive cardiomyopathy** is used. Although the left ventricle is predominantly affected, the right ventricle may be involved, particularly in infancy. The mitral valve can demonstrate systolic anterior motion and mitral insufficiency. Left ventricular outflow tract (LVOT) obstruction occurs in 25% of patients, is dynamic in nature, and may in part be secondary to the abnormal position of the mitral valve as well as the obstructing subaortic hypertrophic cardiac muscle. The cardiac myofibrils and myofilaments demonstrate disarray and myocardial fibrosis.

Typically, systolic function is preserved or even hyperdynamic, although systolic dysfunction may occur late and is a predictor for death or need for cardiac transplant. LVOT obstruction with or without mitral insufficiency may be provoked by physiologic manipulations such as the Valsalva maneuver, positional changes, and physical activity. Frequently, the hypertrophic and fibrotic cardiac muscle demonstrates relaxation abnormalities (diminished compliance), and LV filling may be impaired (diastolic dysfunction).

CLINICAL MANIFESTATIONS

Many patients are asymptomatic; 50% of cases present with a heart murmur or during screening when another family member has been diagnosed with HCM. Symptoms of HCM may include palpitations, chest pain, easy fatigability, dyspnea, dizziness, and syncope. Sudden death is a well-recognized but uncommon manifestation that occurs during physical exertion but may also occur at rest or during sleep. Characteristic physical examination findings include an overactive precordial impulse with a lift or heave, a systolic ejection murmur in the aortic region *not* associated with an ejection click, and an apical blowing murmur of mitral insufficiency.

DIAGNOSIS

The ECG typically demonstrates LV hypertrophy with ST segment and T-wave abnormalities (particularly T-wave inversion in the left precordial leads). Intraventricular conduction delays and signs of ventricular preexcitation **(Wolff-Parkinson-White syndrome)** may be present and should raise the possibility of PRKAG2-related HCM, Danon disease, or Pompe disease. Chest radiography demonstrates normal or mildly increased heart size with a prominence of the left ventricle. Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy (see Fig. 488.3). Doppler interrogation defines, localizes, and quantifies the degree of LVOT obstruction and demonstrates and quantifies the degree of mitral insufficiency and diastolic dysfunction.

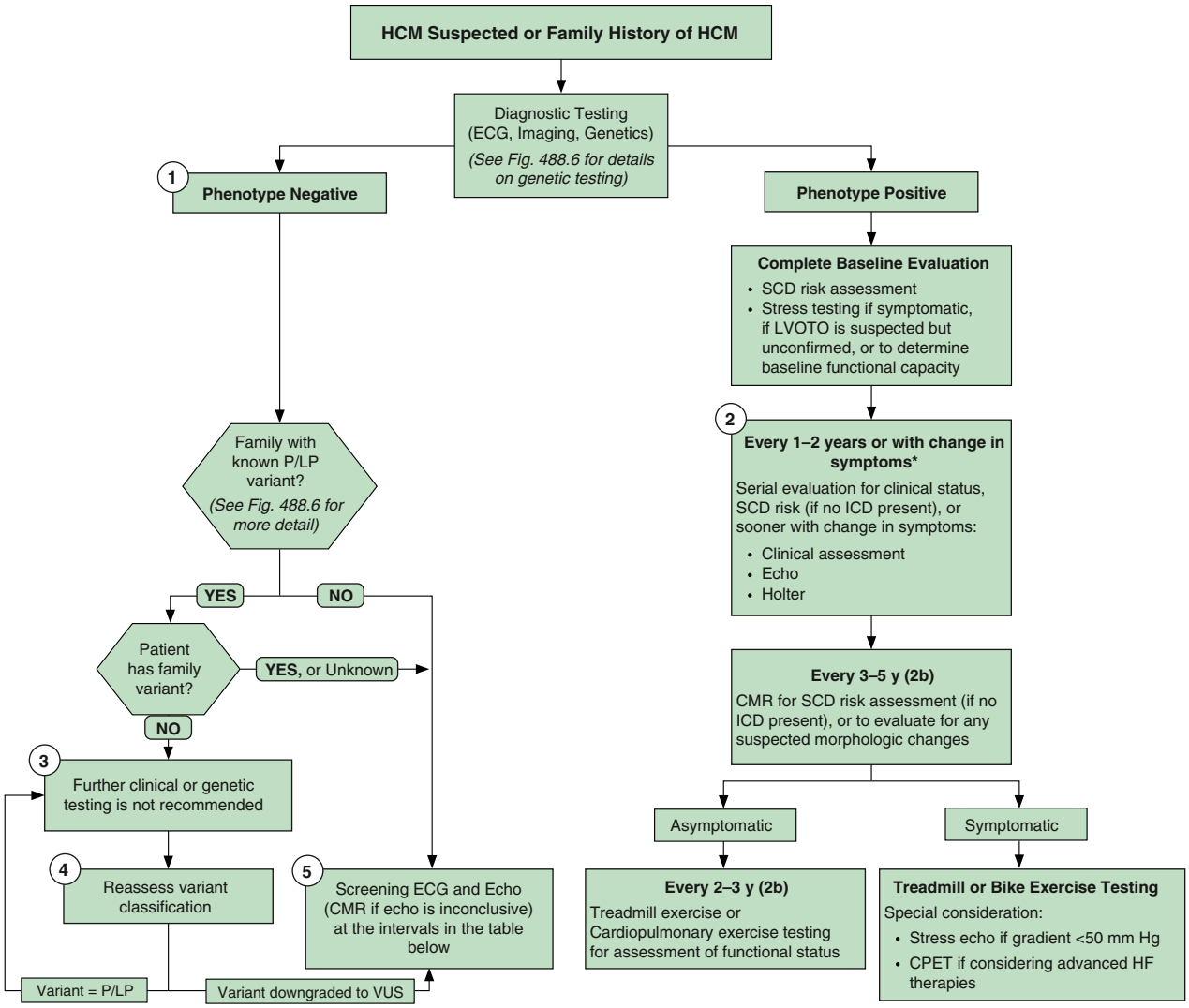
Cardiac catheterization is rarely used in the diagnosis of HCM but may be helpful if there is concern for a **myocardial bridge** (when a coronary artery runs through vs on top of the myocardium) that may be causing intermittent coronary insufficiency during dynamic obstruction. Myocardial bridges can be seen on coronary angiography. Additionally, cardiac catheterization may occasionally be used to better define hemodynamics in patients.

Additional diagnostic studies include metabolic testing, genetic testing for specific syndromes, or genetic testing for pathogenic variants in genes known to cause isolated HCM (see Table 488.3). Clinical genetic testing panels continue to expand. Genetic diagnosis is also useful in identifying at-risk family members who require ongoing surveillance (Figs. 488.5 and 488.6).

PROGNOSIS AND MANAGEMENT

Children <1 year of age or with inborn errors of metabolism or malformation syndromes or those with a mixed HCM/DCM have a significantly poorer prognosis. The risk of sudden death in older patients is greater in those with a personal or family history of cardiac arrest, ventricular tachycardia, exercise hypotension, syncope, or excessive (>3 cm) ventricular wall thickness. Although intrafamilial variability in symptoms occurs, a family history of sudden death is a highly significant predictor of risk. Restriction from competitive sports and strenuous physical activity is highly recommended, and additional recreational exercise activities should be tailored to each individual based on their overall clinical status. β-Adrenergic blocking agents (propranolol, atenolol, metoprolol) or calcium channel blockers (verapamil) may be useful in diminishing LVOT obstruction, modifying LV hypertrophy, and improving ventricular filling. They also confer an antiarrhythmic benefit and may reduce symptoms. In patients with atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be used. Patients with documented, previously aborted sudden cardiac arrest, strong family histories of sudden death, ventricular wall end-diastolic dimensions of ≥3 cm, unexplained syncope, nonsustained ventricular tachycardia, apical aneurysm, ejection fraction ≤50%, or blunted or hypotensive blood pressure response to exercise should be considered for treatment with an **implantable cardioverter-defibrillator** (ICD). Early identification of HCM, family screening/surveillance, appropriate activity restriction, and use of ICDs have greatly reduced the mortality of HCM to approximately 0.5% per year in the modern era.

Innovative interventional procedures have been used to reduce the degree of LVOT obstruction anatomically or physiologically. Dual-chamber pacing, alcohol septal ablation, surgical septal



Screening Asymptomatic First-Degree Relatives of Patients With HCM		
Age of First-Degree Relative	**Initiation of Screening**	**Surveillance Interval**
Children and adolescents from genotype-positive family and/or family with early onset HCM	At the time of diagnosis in another family member	Every 1–2 y
All other children and adolescents	At any time after the diagnosis in the family, but no later than puberty	Every 2–3 y
Adults	At the time of diagnosis in another family member	Every 3–5 y

Fig. 488.5 Algorithm for recommended evaluation and testing modified for HCM. *The interval may be extended, particularly in adult patients who remain stable after multiple evaluations. CMR, Cardiovascular magnetic resonance; CPET, cardiopulmonary exercise test; ECG, electrocardiography/electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVOTO, left ventricular outflow tract obstruction; P/LP, pathogenic or likely pathogenic variant; SCD, sudden cardiac death; VUS, variant of unknown significance. *(Modified from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. J Amer Coll Cardiol. 2020;142:e533–e557, Fig. 1.)*

myomectomy, and mitral valve replacement have all met with some success but are typically reserved for patients with significant symptoms despite medical therapy (Fig. 488.7). Mavacamten, a selective myosin inhibitor, has been an effective therapy in adults. Enzyme replacement therapy for Pompe disease is an effective therapy after birth (see Chapter 107.1). Preliminary trials of in utero enzyme replacement therapy for Pompe disease have also demonstrated efficacy.

First-degree relatives of patients identified as having HCM should be screened with ECG and echocardiogram. Genetic testing is available clinically and is of high utility. It is important first to test the affected individual in the family rather than "at-risk" individuals, because 20–50% of cases of HCM will not demonstrate pathogenic variants in currently available panels of genes. If a causative genetic variant is identified, at-risk members of the family can be effectively tested. In families with HCM without demonstrable pathogenic variants, repeat noninvasive cardiac screening with ECG and echocardiogram should be undertaken in at-risk individuals yearly until young adulthood (age 21 years) and then every 3 years if no prior evidence of HCM is present. Gene-positive but phenotype-negative pediatric patients may remain asymptomatic during childhood but require careful and frequent follow-up.

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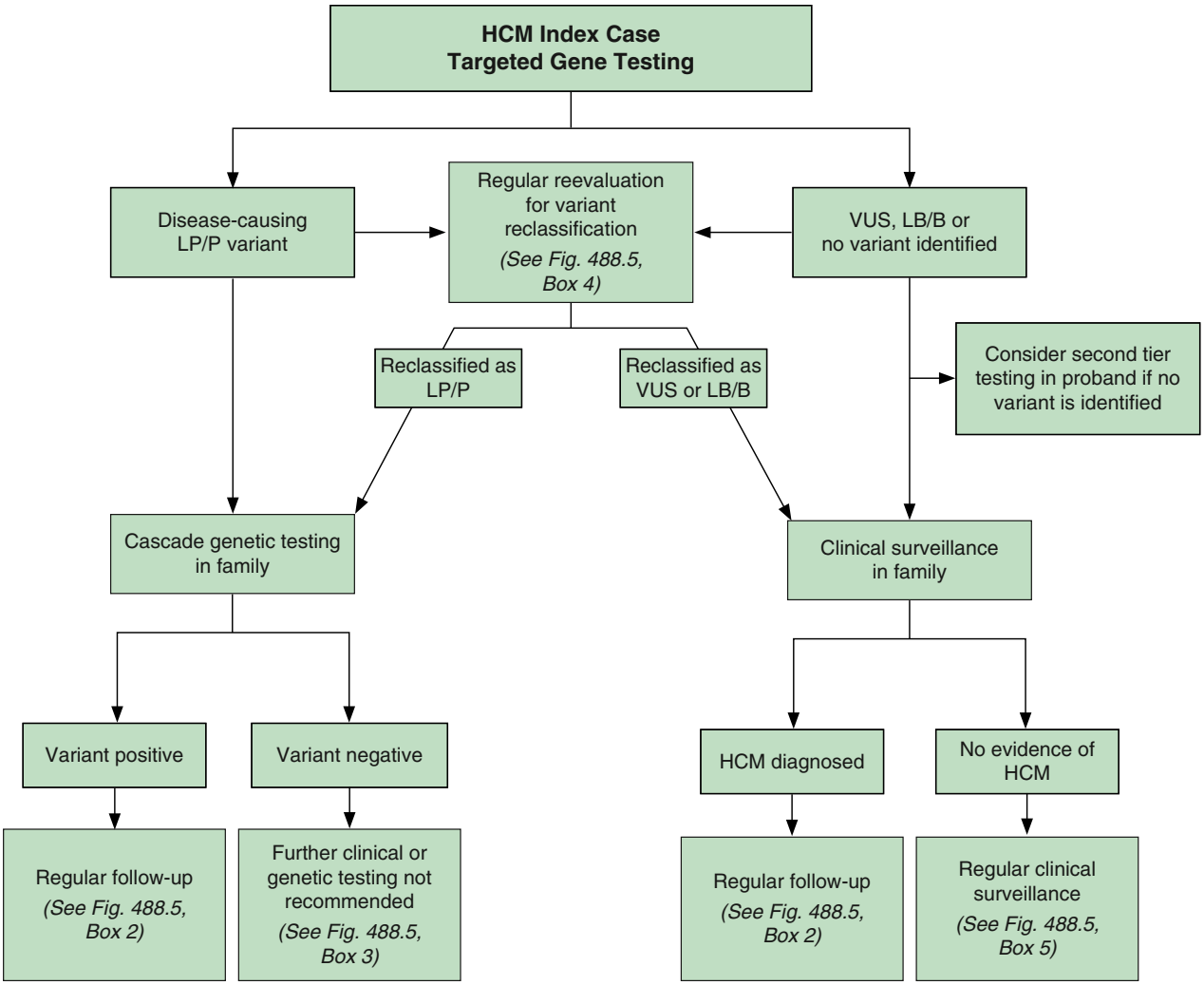

Fig. 488.6 Algorithm for genetic testing processes in HCM. HCM, Hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; VUS, variant of unknown significance. *(Modified from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary. J Amer Coll Cardiol. 2020;142:e533–e557, Fig. 2.)*

488.3 Restrictive Cardiomyopathy

John J. Parent and Stephanie M. Ware

Restrictive cardiomyopathy **(RCM)** accounts for <5% of cardiomyopathy cases. Incidence increases with age and is more common in females. In equatorial Africa, RCM accounts for a large number of deaths. Infiltrative myocardial causes and storage disorders frequently result in associated LV hypertrophy and may represent HCM with restrictive physiology. Noninfiltrative causes include pathogenic variants in genes encoding sarcomeric or cytoskeletal proteins. Although there has been significant success in discovering pathogenic gene variants causing RCM, the majority of cases are considered idiopathic. Potential etiologies include sarcoidosis and Gaucher, Hurler, or Fabry diseases.

PATHOGENESIS

RCM is characterized by normal ventricular chamber dimensions, normal myocardial wall thickness, and preserved systolic function. Dramatic atrial dilation can result from the abnormal ventricular myocardial compliance and high ventricular diastolic pressure. Autosomal dominant inheritance has been demonstrated for families with pathogenic gene variants in sarcomeric and cytoskeletal genes.

CLINICAL MANIFESTATIONS

Abnormal ventricular filling, sometimes referred to as *diastolic heart failure,* is manifest in the systemic venous circulation with edema, hepatomegaly, or ascites. Elevation of left-sided filling pressures results in cough, dyspnea, or pulmonary edema. With activity, patients may experience chest pain, shortness of breath, syncope/near-syncope, or even sudden death. Pulmonary hypertension and pulmonary vascular disease develop and may progress rapidly. Heart murmurs are typically absent, but a gallop rhythm may be prominent. In the presence of pulmonary hypertension, an overactive RV impulse and pronounced pulmonary component of the second heart sound (S_2) are present in RCM.

DIAGNOSIS

The characteristic electrocardiographic finding of prominent P waves (reflective of atrial enlargement) is usually associated with normal QRS voltages and nonspecific ST and T-wave changes. RV hypertrophy occurs in patients with pulmonary hypertension. The chest radiograph may be normal or may demonstrate a prominent atrial shadow and pulmonary vascular redistribution. The echocardiogram is often diagnostic, demonstrating normal-sized ventricles with preserved systolic function and dramatic enlargement of the atria (see Fig. 488.4). Flow and tissue Doppler interrogation reveal abnormal filling parameters. It is critical to differentiate RCM from **constrictive pericarditis**, which can be treated surgically (see Chapter 489.2). MRI may be necessary to demonstrate the thickened or calcified pericardium often present in constrictive pericardial disease.

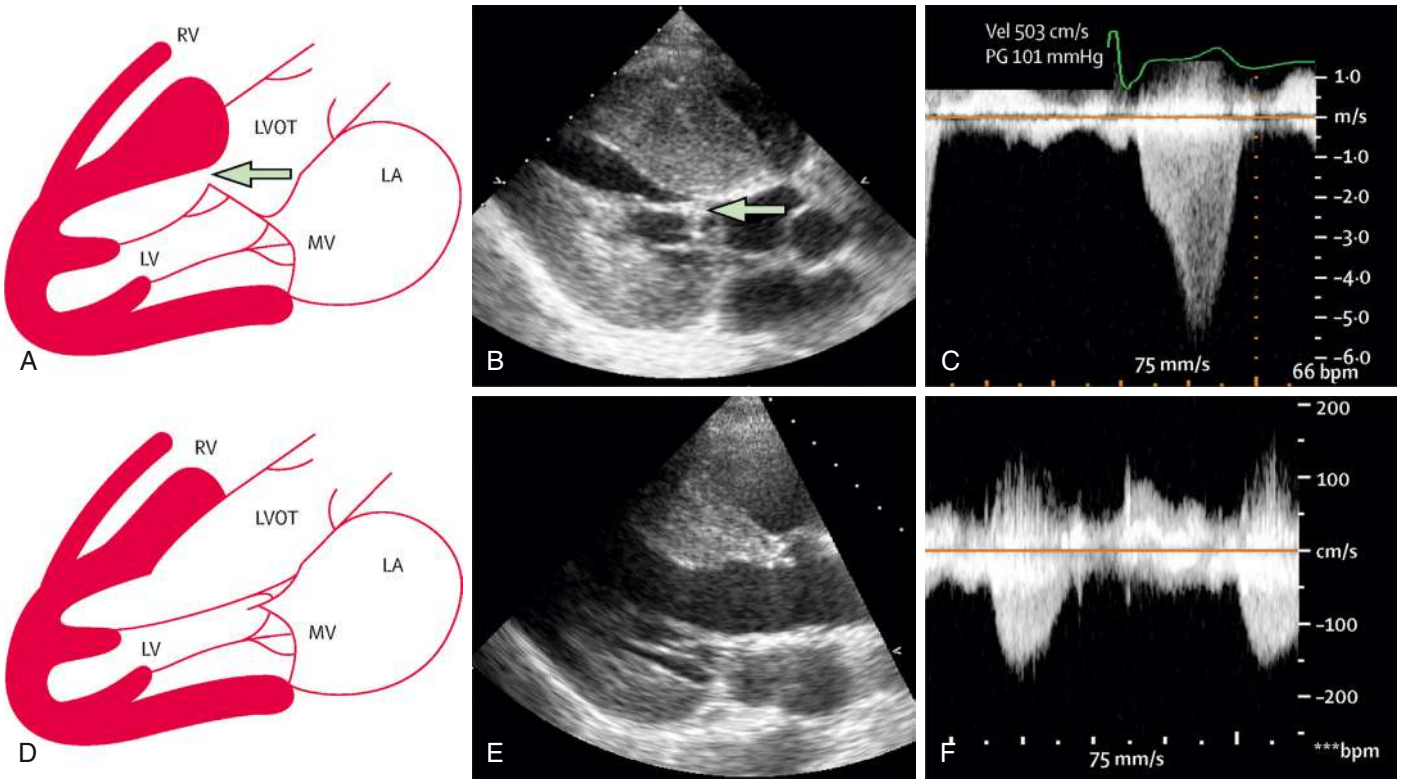

Fig. 488.7 Scheme of septal reduction therapy. **A,** Left ventricular outflow tract (LVOT) obstruction *(arrow)* created by hypertrophied basal septum and systolic anterior motion. **B,** Transthoracic echocardiography with systolic anterior motion *(arrow)*. **C,** Continuous-wave Doppler imaging of dynamic LVOT obstruction. **D,** Schematic finding after septal reduction. **E,** Transthoracic echocardiography after septal reduction procedure. **F,** Absence of LVOT obstruction in continuous-wave Doppler imaging after septal reduction therapy. LA, Left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. *(From Veselka J, Anavekar NS, Charron P. Hypertrophic obstructive cardiomyopathy. Lancet. 2017;389:1253–1264, Fig. 5, p. 1259.)*

PROGNOSIS AND MANAGEMENT

Pharmacologic modalities are of limited use, and the prognosis of patients with RCM is generally poor, with often progressive clinical deterioration. Sudden death is a significant risk, with a 2-year survival of 50%. When signs of heart failure exist, judicious use of diuretics can result in clinical improvement. As a result of the dramatic atrial enlargement and ventricular scarring, these patients are predisposed to the development of atrial tachyarrhythmias, complete heart block, and thromboemboli. Antiarrhythmic agents may be necessary, and anticoagulation with platelet inhibitors or warfarin (Coumadin) is indicated.

Cardiac transplantation is the treatment of choice in many centers for patients with RCM, and the results are excellent in patients without pulmonary hypertension, pulmonary vascular disease, or severe congestive heart failure. Some patients may need bridging to transplant with a VAD if they have elevated pulmonary pressures or significant heart failure.

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488.4 Left Ventricular Noncompaction, Arrhythmogenic Right Ventricular Cardiomyopathy, Endocardial Fibroelastosis, and Takotsubo Cardiomyopathy

John J. Parent and Stephanie M. Ware

Left ventricular noncompaction (LVNC) is characterized by a distinctive trabeculated or spongy-appearing left ventricle commonly associated with LV dysfunction and/or dilation and at times hypertrophy, diastolic dysfunction, and arrhythmias (Fig. 488.8). LVNC may be isolated or associated with structural congenital cardiac defects. Patients may present with signs of heart failure, arrhythmias, syncope, sudden death, or as an asymptomatic finding during screening of family members.

Imaging studies using ultrasound or MRI can demonstrate the characteristic pattern of deeply trabeculated LV myocardium, most characteristically within the apex. ECG findings are nonspecific and include chamber hypertrophy, ST and T-wave changes, or arrhythmias. In some patients, preexcitation is notable, and giant QRS voltages occur in approximately 30% of younger children. Metabolic screening should be considered, especially in young children. Elevated serum lactate and urine 3-methylglutaconic acid may be seen in **Barth syndrome**, an X-linked disorder of phospholipid metabolism caused by a pathogenic variant in the *TAZ* gene. Clinical testing for *TAZ* variants is available and should be considered, especially in males. Patients with mitochondrial disorders frequently demonstrate signs of LVNC. These children are at risk for atrial or ventricular arrhythmias and thromboembolic complications. Treatment includes anticoagulation, antiarrhythmic therapy if needed, and treatment of heart failure if present. In patients refractory to medical therapy, cardiac transplantation has been used successfully.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is relatively uncommon in North America compared with the high prevalence in Europe, especially Italy (see Chapter 484.4). Autosomal dominant inheritance is common. In addition, recessive forms associated with severe ARVC and skin manifestations are known. Comprehensive genetic screening has been reported to identify a cause in up to 50% of cases. ARVC is typically characterized by a dilated right ventricle with fibrofatty infiltration of the RV wall; increasingly, LV involvement is being recognized. Global and regional RV and LV dysfunction and ventricular tachyarrhythmias are the major clinical findings. Syncope or aborted sudden death can occur and should be treated with antiarrhythmic medications and placement of an ICD. In patients with ventricular dysfunction, heart failure management as indicated for patients with DCM may be of use.

Endocardial fibroelastosis (EFE), once an important cause of heart failure in children, is uncommon. The decline in primary EFE is likely related to the abolition of mumps virus infections by immunization practices. Rare familial cases exist, but the causative genes are unknown. Secondary EFE can occur with severe left-sided obstructive lesions such as aortic stenosis or atresia, hypoplastic left heart

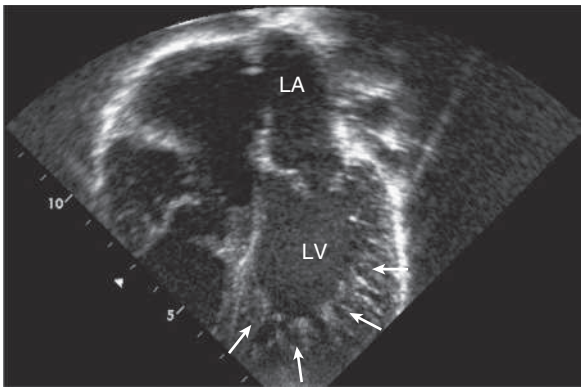

Fig. 488.8 Echocardiogram of a patient with left ventricular noncompaction cardiomyopathy. Apical view showing abnormal trabeculations of left ventricle at the apex *(arrows)*. For comparison, see the smooth-walled LV in Figure 488.2. LA, Left atrium; LV, left ventricle.

syndrome, or coarctation of the aorta. EFE is characterized by an opaque, white, fibroelastic thickening on the endocardial surface of the ventricle, which leads to systolic and/or diastolic dysfunction. Surgical removal of the endocardial fibrosis has been successfully done to improve cardiac function. Standard heart failure management, including transplantation, has been used in the management of EFE.

Takotsubo cardiomyopathy is a reversible stress-induced syndrome associated with transient systolic and diastolic dysfunction and regional ventricular wall motion abnormalities characterized by ventricular apical ballooning. Physical or emotional stress and associated etiologies (see Table 488.2) precipitate transient episodes of chest pain or heart failure. Treatment includes that for heart failure (β blockers, ACE inhibitors, diuretics) and addressing the precipitating event (thyrotoxicosis, pheochromocytoma, drug ingestion).

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488.5 Myocarditis

John J. Parent and Stephanie M. Ware

Acute or chronic inflammation of the myocardium is characterized by inflammatory cell infiltrates, myocyte necrosis, or myocyte degeneration and may be caused by infectious, connective tissue, granulomatous, toxic, immune, or idiopathic processes. There may be associated systemic manifestations of the disease, and occasionally the endocardium or pericardium is involved. Patients may be asymptomatic, have nonspecific prodromal symptoms, or present with overt congestive heart failure, compromising arrhythmias, or sudden death. It is assumed that viral infections are the most common etiology, although myocardial toxins, drug exposures, hypersensitivity reactions, and immune disorders may also lead to myocarditis (Table 488.7).

ETIOLOGY AND EPIDEMIOLOGY

Viral Infections

Coxsackievirus and other enteroviruses, adenovirus, parvovirus B19, Epstein-Barr virus, parechovirus, influenza virus, and cytomegalovirus are the most common causative agents in children. COVID-19 infections, particularly during multisystem inflammatory syndrome in children (MIS-C) and, rarely, after mRNA COVID-19 vaccinations, have been associated with myocarditis. In Asia, hepatitis C virus appears to be significant as well. The true incidence of viral myocarditis is unknown because mild cases probably go undetected. The disease is typically sporadic but may be epidemic. Manifestations are, to some degree, age dependent: in neonates and young infants, viral myocarditis can be fulminant; in children, it often occurs as an acute, myopericarditis with heart failure; and in older children and adolescents, it may present with signs and symptoms of acute or chronic heart failure or chest pain.

Table 488.7 Etiology of Myocarditis

INFECTIOUS CAUSES
Viral: adenoviruses, echoviruses, enteroviruses (e.g., coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza virus, parvovirus B19, SARS-CoV-2 (COVID-19) disease and vaccine, smallpox vaccine
Bacterial: *Borrelia burgdorferi* (Lyme disease), *Chlamydia, Corynebacterium diphtheriae, Legionella, Mycobacterium tuberculosis, Mycoplasma, Staphylococcus,* streptococcus A, *Streptococcus pneumoniae,* Whipple disease
Fungal: *Actinomyces, Aspergillus, Candida, Cryptococcus*
Helminthic: *Echinococcus granulosus, Trichinella spiralis*
Protozoal: *Toxoplasma gondii, Trypanosoma cruzi*
Rickettsial: *Coxiella burnetii, Rickettsia typhi*
Spirochetal: *Borrelia burgdorferi, Leptospira, Treponema pallidum*
AUTOIMMUNE DISEASES
Rheumatic fever, celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematosus, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis
HYPERSENSITIVITY REACTIONS
Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
TOXIC REACTIONS TO DRUGS
Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab, immune checkpoint inhibitors
TOXIC
Ethanol, snakebite, scorpion bite, electric shock, spider bite
OTHER CAUSES
Arsenic, copper, iron, radiotherapy, thyrotoxicosis, immune modulation

Adapted from Canter CE, Simpson KE. Diagnosis and treatment of myocarditis in children in the current era. *Circulation.* 2014;129:115–128, Table 1.

Bacterial Infections

Bacterial myocarditis has become much less common with the advent of advanced public health measures, which have minimized infectious causes such as diphtheria. Diphtheritic myocarditis is unique because bacterial toxin may produce circulatory collapse and toxic myocarditis characterized by atrioventricular block, bundle branch block, or ventricular ectopy (see Chapter 233). Lyme disease may present as myocarditis; rheumatic fever (poststreptococcal) may also manifest with valve, myocardium, and pericardium involvement. Any overwhelming systemic bacterial infection can manifest with circulatory collapse and shock with evidence of myocardial dysfunction, characterized by tachycardia, gallop rhythm, and low cardiac output. Additional nonviral infectious causes of myocarditis include rickettsiae, protozoa, parasitic infections, and fungal disease.

PATHOPHYSIOLOGY

Myocarditis is characterized by myocardial inflammation, injury or necrosis, and ultimately fibrosis. Cardiac enlargement and diminished systolic function are a direct result of the myocardial damage. Typical signs of congestive heart failure occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death. Viral myocarditis may also become a chronic process, with persistence of viral nucleic acid in the myocardium and the perpetuation of chronic inflammation secondary to altered host immune response, including activated T lymphocytes (cytotoxic and natural killer cells) and antibody-dependent cell-mediated damage. Additionally, persistent viral infection may alter the expression of major histocompatibility complex (MHC) antigens with resultant exposure of neoantigens to the immune system. Some viral proteins share antigenic epitopes with host cells, resulting in autoimmune damage to the antigenically related myocyte. Cytokines such as tumor necrosis factor-α and interleukin-1 are inhibitors of myocyte response to adrenergic stimuli and result in diminished cardiac function. The final result of viral-associated inflammation can be DCM.

CLINICAL MANIFESTATIONS

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end-organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near-syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and apical systolic murmur of mitral insufficiency. In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

DIAGNOSIS

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest radiographs in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, LV dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis (Table 488.8 and Fig. 488.9).

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis or if unusual forms of cardiomyopathy are strongly suspected, such as storage diseases or mitochondrial defects. Nonspecific tests include erythrocyte sedimentation rate, CPK isoenzymes, cardiac troponin I, and BNP levels. A novel microRNA derived from type 17 helper (Th17) cells may be another useful specific test for viral myocarditis.

DIFFERENTIAL DIAGNOSIS

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 488.2).

TREATMENT

Primary therapy for acute myocarditis is supportive. Acutely, the use of inotropic agents, preferably milrinone, should be considered but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with VAD implantation or ECMO may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, β blockers, ACE inhibitors, and ARBs are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (e.g., amiodarone) should be administered and ICD placement considered if persistent after a period of recovery is observed.

Table 488.8 MRI Findings Suggestive of Myocarditis

- T2-weighted edema (global or regional)
- Regional hyperemia/capillary leak by early gadolinium enhancement ratio (EGEr)
- Myocardial fibrosis or necrosis on late gadolinium enhancement (LGE)
- Features often present in a midmyocardial, subepicardial, and nonvascular distribution
- Repeat MRI if no *early* MRI evidence present but clinical manifestation suggests myocarditis

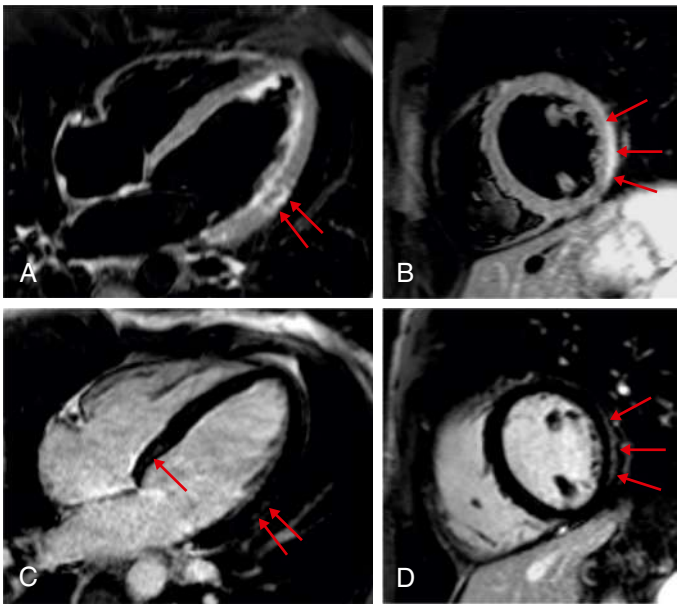

Fig. 488.9 MRI findings in patients with myocarditis. Cardiac MR images of a young patient presenting with acute chest pain syndrome caused by acute myocarditis. (**A**) Long-axis and (**B**) short-axis T2-weighted images demonstrating focal myocardial edema in subepicardium of left midventricular lateral wall *(red arrows)*. Corresponding (**C**) long-axis and (**D**) short-axis T1-weighted images demonstrate the presence of typical late gadolinium enhancement in subepicardium of left midventricular lateral wall and basal septum *(red arrows)*. *(From Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59:779–792, Fig. 3, p. 783.)*

Immunomodulation of patients with myocarditis is controversial. Intravenous immunoglobulin (IVIG) may have a role in the treatment of acute or fulminant myocarditis, and corticosteroids have been reported to improve cardiac function, but this remains controversial in children. Relapse has been noted in patients receiving immunosuppression who were weaned from therapy. There are no studies to recommend specific antiviral therapies for myocarditis.

If there is an identifiable and treatable condition, its specific therapy should be employed. If a medication is the etiology, it should be withdrawn and an alternative drug added if needed.

PROGNOSIS

The prognosis of symptomatic acute enteroviral myocarditis in newborns is poor, with a 75% mortality. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to the need for cardiac transplantation; recovery of ventricular function, however, has been reported in 10–50% of patients.

The prognosis for COVID-19 immunization–associated myocarditis is excellent with full recovery noted by 90 days. Patients with COVID-19 requiring intensive care unit (ICU) admission and those with MIS-C must be followed by a pediatric cardiologist (including follow-up echocardiography) and refrain from exercise for 3-6 months. Return to full activity requires clearance from a cardiologist.

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Chapter 489
Diseases of the Pericardium

John J. Parent and Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the *pericardium,* which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of

CLINICAL MANIFESTATIONS

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end-organ involvement such as hepatitis or aseptic meningitis.

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Primary therapy for acute myocarditis is supportive. Acutely, the use of inotropic agents, preferably milrinone, should be considered but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with VAD implantation or ECMO may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, β blockers, ACE inhibitors, and ARBs are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (e.g., amiodarone) should be administered and ICD placement considered if persistent after a period of recovery is observed.

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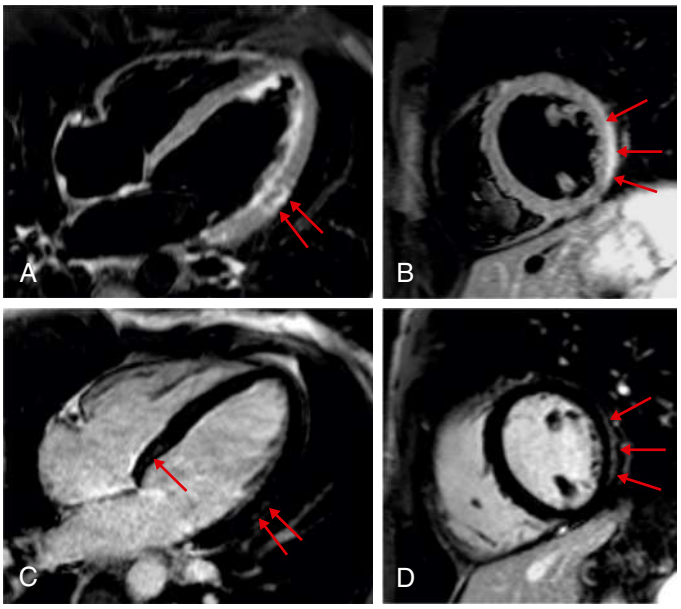

Fig. 488.9 MRI findings in patients with myocarditis. Cardiac MR images of a young patient presenting with acute chest pain syndrome caused by acute myocarditis. (**A**) Long-axis and (**B**) short-axis T2-weighted images demonstrating focal myocardial edema in subepicardium of left midventricular lateral wall *(red arrows)*. Corresponding (**C**) long-axis and (**D**) short-axis T1-weighted images demonstrate the presence of typical late gadolinium enhancement in subepicardium of left midventricular lateral wall and basal septum *(red arrows)*. *(From Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59:779–792, Fig. 3, p. 783.)*

Immunomodulation of patients with myocarditis is controversial. Intravenous immunoglobulin (IVIG) may have a role in the treatment of acute or fulminant myocarditis, and corticosteroids have been reported to improve cardiac function, but this remains controversial in children. Relapse has been noted in patients receiving immunosuppression who were weaned from therapy. There are no studies to recommend specific antiviral therapies for myocarditis.

If there is an identifiable and treatable condition, its specific therapy should be employed. If a medication is the etiology, it should be withdrawn and an alternative drug added if needed.

PROGNOSIS

The prognosis of symptomatic acute enteroviral myocarditis in newborns is poor, with a 75% mortality. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to the need for cardiac transplantation; recovery of ventricular function, however, has been reported in 10–50% of patients.

The prognosis for COVID-19 immunization–associated myocarditis is excellent with full recovery noted by 90 days. Patients with COVID-19 requiring intensive care unit (ICU) admission and those with MIS-C must be followed by a pediatric cardiologist (including follow-up echocardiography) and refrain from exercise for 3-6 months. Return to full activity requires clearance from a cardiologist.

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Chapter 489
Diseases of the Pericardium

John J. Parent and Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the *pericardium,* which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of

conditions, often as a manifestation of a systemic illness, and can result in serious, even life-threatening, cardiac compromise (Table 489.1).

489.1 Acute Pericarditis

John J. Parent and Stephanie M. Ware

Inflammation of the pericardium may have only minor pathophysiologic consequences in the absence of significant fluid accumulation in the pericardial space. When the amount of fluid in the nondistensible pericardial space becomes excessive, pressure within the pericardium increases and is transmitted to the heart, resulting in impaired filling by compressing the chambers (atria or ventricles). Although small to moderate amounts of **pericardial effusion** can be well tolerated and clinically silent, once the noncompliant pericardium has been distended maximally, any further fluid accumulation causes abrupt impairment of cardiac filling, and this can impair cardiac output and is termed **cardiac tamponade**. When untreated, tamponade can lead to shock and death. Pericardial effusions may be serous/transudative, exudative/purulent, fibrinous, or hemorrhagic.

Pericarditis may present without an obvious pericardial effusion on echocardiography. In addition, pericarditis may be associated with myocarditis (**myopericarditis**), in which case either pericarditis or myocarditis may be the dominant finding.

CLINICAL MANIFESTATIONS

The most common symptom of acute pericarditis is chest pain, typically described as sharp/stabbing, positional, radiating, worse with inspiration, and relieved by sitting upright, leaning forward, or prone. Cough, fever, dyspnea, abdominal pain, and vomiting are nonspecific symptoms associated with pericarditis. Additionally, signs and symptoms of organ system involvement may occur in the presence of generalized systemic disease.

Muffled or distant heart sounds, tachycardia, narrow pulse pressure, jugular venous distention, and a pericardial friction rub provide clues to the diagnosis of acute pericarditis. Cardiac tamponade is recognized by the excessive fall of systolic blood pressure (>10 mm Hg) with inspiration. This pulsus paradoxus can be assessed by careful auscultatory blood pressure determination (automated blood pressure cuffs are inadequate), arterial pressure line waveform, or pulse oximeter tracing inspection. Doppler assessment during echocardiography can also indirectly suggest pulsus paradoxus is present. Conditions other than cardiac tamponade that may result in pulsus paradoxus include severe dyspnea, obesity, and positive pressure ventilator support.

Table 489.1 Etiology of Pericardial Disease

CONGENITAL
Absence (partial, complete)
Cysts
Mulibrey nanism (*TRIM 37* gene variant)
Camptodactyly-arthropathy–coxa vara–pericarditis syndrome (*PRG4* gene variant)
Myhre syndrome (*SMAD4* gene variant)
INFECTIOUS
Viral: coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps, COVID-19, and mRNA COVID-19 and HPV vaccines
Bacterial: *Haemophilus influenzae,* streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, *Listeria,* leptospirosis, tuberculosis, Q fever, salmonella
Immune complex mediated: meningococcus, *H. influenzae*
Fungal: actinomycosis, histoplasmosis
Parasitic: toxoplasmosis, echinococcosis
NONINFECTIOUS
Idiopathic
Systemic inflammatory diseases: acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, eosinophilic granulomatosis with polyangiitis, Behçet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis
Metabolic: uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency
Traumatic: surgical, catheter perforation, blunt trauma
Postpericardiotomy syndrome
Oncologic: lymphomas, leukemia, radiation therapy, primary pericardial tumors

DIAGNOSIS

The electrocardiogram is often abnormal in acute pericarditis, although the findings are nonspecific. Low-voltage QRS amplitude may be seen as a result of pericardial fluid accumulation. Tachycardia and abnormalities of the ST segments (diffuse ST segment elevation), PR segments, and T waves (inversion or flattening) may be present as well. Elevated troponin levels may be present in myopericarditis.

Although the chest x-ray findings in a patient with pericarditis without effusion are usually normal in the presence of a significant effusion, cardiac enlargement will be seen and the cardiac contour may be unusual (Erlenmeyer flask or water bottle appearance) (Fig. 489.1). Echocardiography is the most sensitive technique for identifying the size and location of a pericardial effusion. Compression and collapse of the right atrium and/or right ventricle are present with cardiac tamponade (Fig. 489.2). Abnormal diastolic filling parameters have also been described in cases of tamponade. Advanced imaging modalities like computed tomography or cardiac magnetic resonance imaging are useful for diagnosis in unclear cases (Fig. 489.3).

DIFFERENTIAL DIAGNOSIS

Chest pain similar to that present in pericarditis can occur with lung diseases, especially pleuritis, and with gastroesophageal reflux or costochondritis, with the latter being reproducible on palpation. Pain related to myocardial ischemia is usually more severe and prolonged and occurs with exercise, allowing distinction from pericarditis-induced pain. The presence of pericardial effusion on echocardiography is highly suggestive of pericarditis but does not determine the etiology.

Infectious Pericarditis

A number of viral agents are known to cause pericarditis, and the clinical course of the majority of these infections is mild and spontaneously resolving. The term *acute benign pericarditis* is synonymous for viral pericarditis. Agents identified as causing pericarditis include the enteroviruses, influenza, adenovirus, respiratory syncytial virus, and parvovirus. Because the course of this illness is usually benign, symptomatic treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is often sufficient. Persistent or early recurrence episodes may need courses of colchicine or, rarely, corticosteroids. Anakinra and the interleukin-1

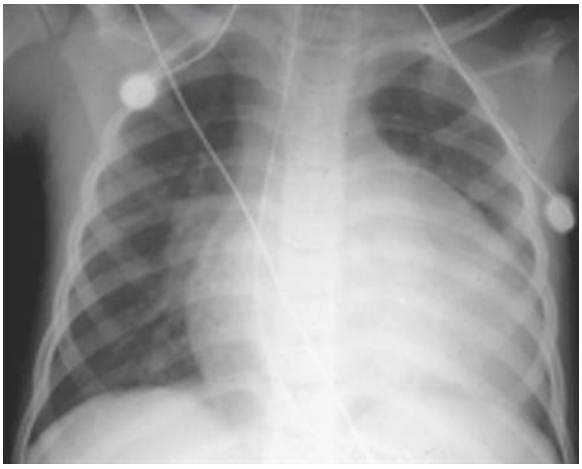

Fig. 489.1 "Water bottle" silhouette. This chest radiograph shows marked cardiomegaly, also known as a water bottle silhouette, which is seen in the presence of large pericardial effusions. Also note the associated pulmonary edema from associated high left atrial and left ventricular filling pressures. *(Courtesy Dr. Steven M. Selbst, Wilmington, DE; from Durani Y, Giordani K, Goudie BW. Myocarditis and pericarditis in children. Pediatr Clin North Am 2010;57:1281–1303, Fig. 7.)*

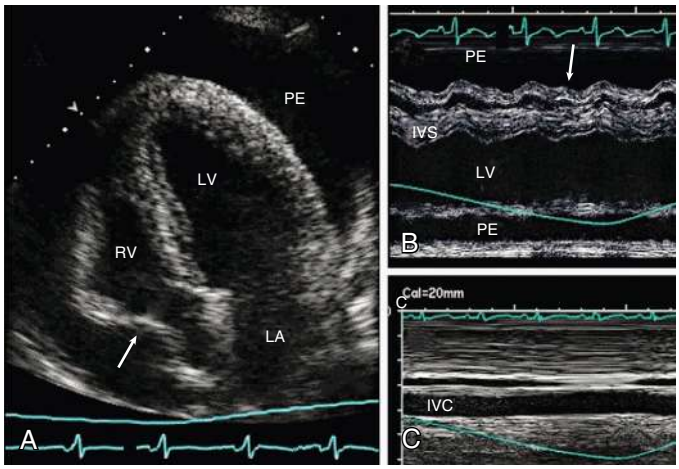

Fig. 489.2 Echocardiographic images of large pericardial effusion with features of tamponade. **A,** Apical four-chamber view of LV, LA, and RV that shows large PE with diastolic right atrial collapse *(arrow).* **B,** M-mode image with cursor placed through RV, IVS, and LV in parasternal long axis. The view shows circumferential PE with diastolic collapse of RV free wall *(arrow)* during expiration. **C,** M-mode image from subcostal window in the same patient that shows IVC plethora without inspiratory collapse. IVC, Inferior vena cava; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PE, pericardial effusion; RV, right ventricle. *(From Troughton RW, Asher CR, Klein AL. Pericarditis. Lancet. 2004;363:717–727.)*

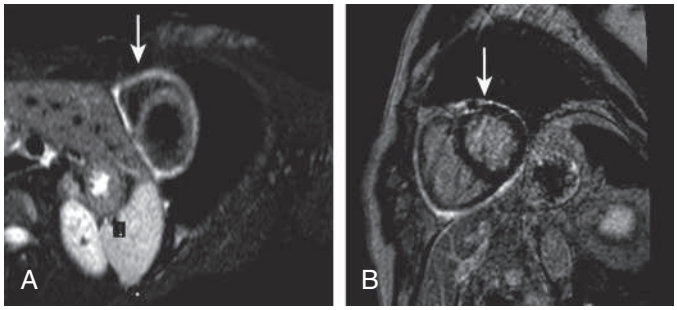

Fig. 489.3 Cardiac magnetic resonance T2 STIR (**A**) and delayed gadolinium (**B**) sequences showing enhancement of the pericardium signifying acute or active inflammation *(arrow). (Modified from Chetrit M, Xu B, Kwon DH, et al: Imaging-guided therapies for pericardial diseases. JACC: Cardiovascular Imaging. 2019;13(6):1422–1437; Fig. 1E and 1F, p. 1424.)*

cytokine trap agent rilonacept have been effective in colchicine-nonresponsive acute or recurrent pericarditis. Patients with large effusions and tamponade may require pericardiocentesis. Presumed viral but often idiopathic pericarditis may have an autoimmune component. Up to 30% of patients may have recurrences of pericarditis. Treatment *and* prevention of recurrences with colchicine improve symptoms and avoid recurrences in most of these patients. If the condition becomes chronic or relapsing, surgical pericardiectomy or creation of a pericardial window may be necessary.

Echocardiography is useful in differentiating pericarditis from *myocarditis,* which will show evidence of diminished myocardial contractility or valvular dysfunction (see Chapter 488.5). Pericarditis and myocarditis may occur together in some cases of viral infection.

Purulent pericarditis, often caused by bacterial infections, has become much less common with the advent of new immunizations for *Haemophilus influenzae* and pneumococcal disease. Historically, purulent pericarditis was seen in association with severe pneumonias, epiglottitis, meningitis, or osteomyelitis. Patients with purulent pericarditis are acutely ill. Unless the infection is recognized and treated expeditiously, the course can be fulminant, leading to tamponade and death. **Tuberculous pericarditis** is rare in developed countries but can be a relatively common complication of HIV infection in regions where tuberculosis is endemic and access to antiretroviral therapy is limited. **Immune complex–mediated pericarditis** is a rare complication that may result in a nonpurulent (sterile) effusion after systemic bacterial infections such as meningococcus or *Haemophilus.*

Noninfectious Pericarditis

Systemic inflammatory diseases such as autoimmune, rheumatologic, and connective tissue disorders may involve the pericardium and result in serous pericardial effusions. Pericardial inflammation may be a component of the type II hypersensitivity reaction seen in patients with acute rheumatic fever. It is often associated with rheumatic valvulitis and responds quickly to antiinflammatory agents, including corticosteroids. Tamponade is quite uncommon (see Chapters 229.1 and 487).

Juvenile idiopathic arthritis, usually systemic-onset disease, can manifest with pericarditis. Differentiating rheumatoid pericardial inflammation from that seen with systemic lupus erythematosus is difficult and requires careful rheumatologic evaluation. Aspirin and corticosteroids can result in rapid resolution of a pericardial effusion but may be needed on a chronic basis to prevent relapse. Many of the autoinflammatory recurrent fever syndromes present with pericarditis, usually with other manifestations of those disorders (see Chapter 204).

Patients with chronic renal failure or hypothyroidism may have pericardial effusions. Clinical suspicion warrants careful screening with physical examination and, if indicated, imaging studies during the course of their illness.

Especially common in referral centers with hematology/oncology units is the presence of pericardial effusion related to neoplastic disease. Conditions resulting in effusion include Hodgkin disease, lymphomas, and leukemia. Radiation therapy directed to the mediastinum of patients with malignancy can result in pericarditis and, later, constrictive pericardial disease.

The **postpericardiotomy syndrome** occurs in patients who have undergone cardiac surgery and is characterized by fever, lethargy, anorexia, irritability, and chest/abdominal discomfort beginning 1-4 weeks postoperatively (see Table 483.2 in Chapter 483). There can be associated pleural effusions. Postpericardiotomy syndrome is effectively treated with aspirin, NSAIDs, colchicine, and in severe cases, corticosteroids. Pericardial drainage is necessary in those patients with cardiac tamponade.

In many patients the etiology of pericarditis is not known. Approximately 30% of these patients have multiple occurrences and are treated with colchicine to reduce the risk of recurrent pericarditis. Other less frequently used treatments have included NSAIDs and corticosteroids. Refractory idiopathic recurrent pericarditis may require pericardiectomy; anakinra and rilonacept have demonstrated promise for difficult-to-treat patients.

489.2 Constrictive Pericarditis

John J. Parent and Stephanie M. Ware

Rarely, chronic pericardial inflammation can result in fibrosis, calcification, and thickening of the pericardium. Pericardial scarring may lead to impaired cardiac distensibility and filling and is termed *constrictive pericarditis.* Constrictive pericarditis can result from recurrent or chronic pericarditis, cardiac surgery, or radiation to the mediastinum as a treatment for malignancies, most often Hodgkin disease or lymphoma.

Clinical manifestations of systemic venous hypertension predominate in cases of restrictive pericarditis. Jugular venous distention, peripheral edema, hepatomegaly, and ascites may precede signs of more significant cardiac compromise, such as tachycardia, hypotension, and pulsus paradoxus. A pericardial knock, rub, and distant heart sounds might be present on auscultation. Abnormalities of liver function tests, hypoalbuminemia, hypoproteinemia, and lymphopenia may be present. On occasion, chest radiographs demonstrate calcifications of the pericardium.

Constrictive pericarditis may be difficult to distinguish clinically from restrictive cardiomyopathy because both conditions result in impaired myocardial filling (see Chapter 488.3). Echocardiography may be helpful in distinguishing constrictive pericardial disease from restrictive cardiomyopathy, but cardiac MRI and CT are more sensitive in detecting abnormalities of the pericardium. In rare cases, exploratory thoracotomy with direct examination of the pericardium may be required to confirm the diagnosis.

Although acute pericardial constriction is reported to respond to antiinflammatory agents, the more typical chronic constrictive pericarditis will respond only to pericardiectomy with extensive resection of the pericardium.

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Chapter 490

Tumors of the Heart

John J. Parent and Stephanie M. Ware

Although cardiac tumors occur rarely in pediatric patients, they may result in serious hemodynamic or electrophysiologic abnormalities depending on tumor type and location.

The vast majority of tumors originating from the heart are benign. **Rhabdomyomas** are the most common pediatric cardiac tumors and are associated with tuberous sclerosis in 70–95% of cases (see Chapter 636.2). Rhabdomyomas may occur at any age, from fetal life through late adolescence. They are often multiple, can occur in any cardiac chamber, and originate within the myocardium, often extending into the atrial or ventricular cavities (Fig. 490.1). Depending on their location and size, rhabdomyomas can result in inflow or outflow obstruction, leading to cyanosis or cardiac failure; many are asymptomatic. Atrial and ventricular arrhythmias have been reported with rhabdomyomas, and on occasion, ventricular preexcitation (Wolff-Parkinson-White syndrome) is present on electrocardiogram (ECG).

Fibromas are the second most common pediatric cardiac tumor and, in contrast to rhabdomyomas, are usually solitary and intramyocardial. The size and location of fibromas can lead to heart failure, cyanosis, or rhythm disturbances. Loss of the tumor suppressor *PTCH1* is associated with the development of cardiac fibromas in sporadic cases. There is an increased incidence in patients with **Gorlin syndrome** (3%).

Myxomas, the most common cardiac tumor seen in adults, occur infrequently in the pediatric population. Myxomas are predominantly intraatrial, appear pedunculated, and are rather mobile (Fig. 490.2); however, they may also be ventricular (Fig. 490.3). They may cause obstruction to inflow or outflow and may present with a murmur, heart failure, or syncope. On occasion, atrial myxomas are associated with systemic symptoms of fever, malaise, and arthralgia. **Carney complex** is a familial autosomal dominant multiple neoplasia (often endocrine: pituitary adenoma, thyroid, testis, ovarian) and lentiginosis syndrome in which cardiac myxomas can occur at a young age in any or all cardiac chambers. Pathogenic variants in the *PRKAR1A* gene are causative in some families.

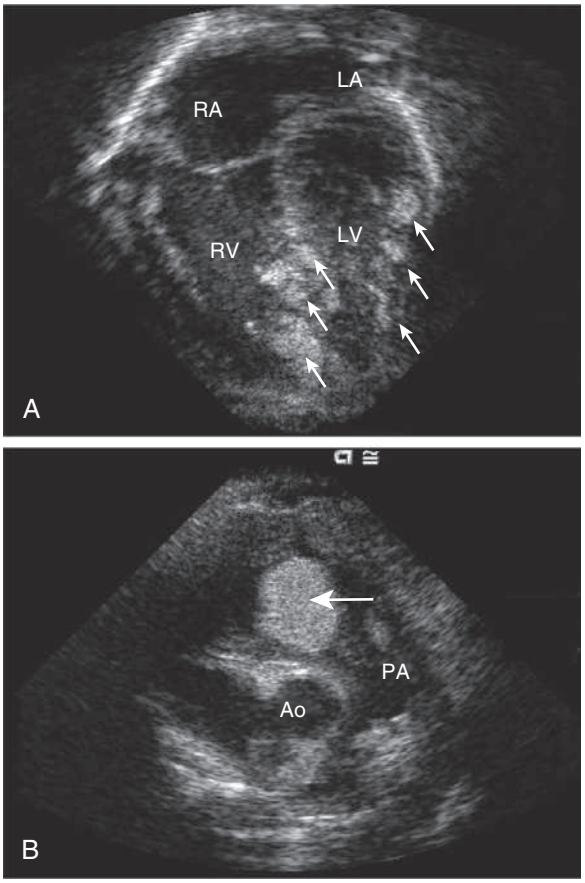

Fig. 490.1 Echocardiograms demonstrating rhabdomyomas. **A,** Apical four-chamber view showing multiple rhabdomyomas *(arrows)* within the septum and left ventricular myocardium. **B,** Short-axis view showing a large rhabdomyoma *(arrow)* extending into the right ventricular outflow tract. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

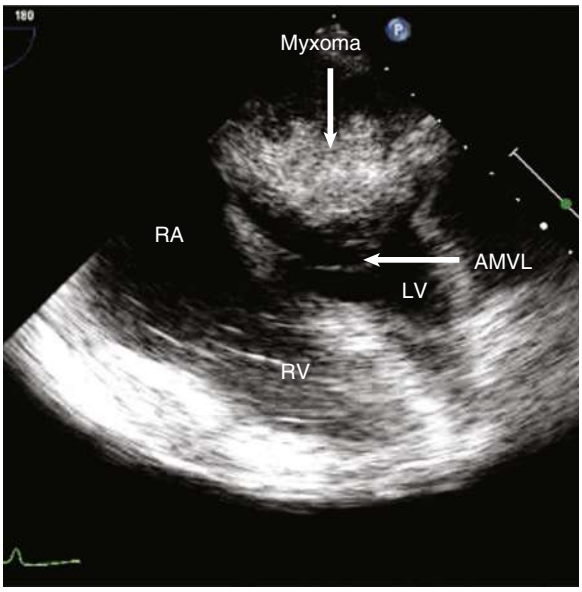

Fig. 490.2 A large left atrial myxoma prolapsing across the mitral valve, resulting in heart failure symptoms. AMVL, anterior mitral valve leaflet; LV, left ventricle; RA, right atrium; RV, right ventricle. *(From Zipes DP, Libby P, Bonow RO, et al., eds. Braunwald's Heart Disease, 11th ed. Philadelphia: Elsevier; 2019, Fig. 95.8, p. 1871.)*

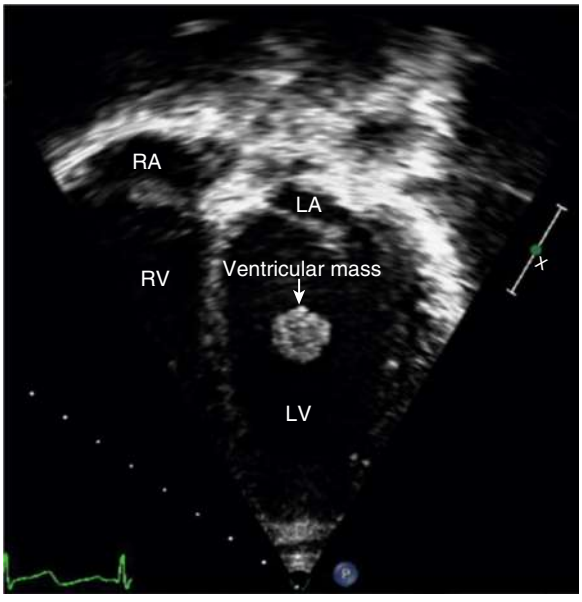

Fig. 490.3 Left ventricular myxoma. TTE apical four-chamber view of mass within the left ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. *(From Schroeder L, Zyblewski S, Forbus G, et al. Left ventricular myxoma. J Pediatr. 2016;168:249–249.e2, Fig. 1.)*

Other benign tumors include hemangiomas, Purkinje cell tumors, papillomas, lipomas, and mesotheliomas. Depending on their location, these benign tumors can result in valvular function abnormalities, myocardial dysfunction, or heart block and other arrhythmias.

Malignant pediatric cardiac tumors are much less common than benign tumors; the majority of such malignancies are sarcomas, including angiosarcomas, rhabdosarcomas, or fibrosarcomas. Lymphomas and pheochromocytomas are reported but rare. Tumors originating from noncardiac sources that invade, extend, or metastasize to the heart are more frequently seen than primary malignant cardiac tumors. In pediatric patients, Wilms tumor and lymphoma/leukemia are the most common causes of such secondary tumors.

Although the manifestations of cardiac tumors in pediatric patients are protean, when a tumor is suspected, noninvasive imaging with echocardiography and/or MRI may be diagnostic and can determine tumor type, location, extent, and hemodynamic impact. ECG and Holter studies are valuable adjuncts when rhythm abnormalities are suspected. Cardiac catheterization is rarely indicated but may be used to confirm tumor location, assess intracardiac hemodynamics, and perform biopsy for histologic assessment. Such risks as blood loss, perforation, arrhythmia, and vessel injury should be considered when discussing catheterization and biopsy.

Because the natural history of rhabdomyomas is one of spontaneous diminution or complete resolution, treatment of the majority of cardiac tumors in pediatric patients is usually unnecessary. *Everolimus,* an inhibitor of the mammalian target of rapamycin (mTOR), may enhance resolution in symptomatic patients with cardiac rhabdomyomas. Careful clinical follow-up and imaging are important. **Antiarrhythmic medications** may be prescribed to control rhythm disorders. Surgical removal of a cardiac tumor may be indicated to relieve obstruction, improve myocardial or valve function, or control arrhythmias. **Heart transplantation** has been performed in cases of unresectable tumors with significant hemodynamic compromise. Wilms tumors extending from the inferior vena cava into the atrium may require cardiopulmonary bypass support during the course of primary resection of the renal tumor. Radiation or chemotherapy can improve cardiac function in rare cases of lymphoma or leukemia compressing the heart with hemodynamic compromise.

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Section 7

Cardiac Therapeutics

Chapter 491

Heart Failure

Danielle S. Burstein and Joseph W. Rossano

The International Society for Heart and Lung Transplantation (ISHLT) defines heart failure as follows:

> A clinical and pathological syndrome that results from ventricular dysfunction, volume, or pressure overload, alone or in combination. It leads to characteristic signs and symptoms, such as poor growth, feeding difficulties, respiratory distress, exercise intolerance, and fatigue, and is associated with circulatory, neurohormonal, and molecular abnormalities. Heart failure has numerous etiologies that are a consequence of cardiac and noncardiac disorders, either congenital or acquired.

PATHOPHYSIOLOGY

The heart can be viewed as a pump with an output proportional to its filling volume and inversely proportional to the resistance against which it pumps. As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached and cardiac output can no longer be augmented (the **Frank-Starling principle**; Fig. 491.1). The increased stroke volume obtained in this manner is a result of stretching of myocardial fibers, but it also results in increased wall tension, which elevates myocardial oxygen consumption. Hearts working under various types of stress function along different Frank-Starling curves. Cardiac muscle with compromised intrinsic contractility requires a greater degree of dilation to produce increased stroke volume and does not achieve the same maximal cardiac output as normal myocardium does. If a cardiac chamber is already dilated because of a lesion causing increased preload (e.g., a left-to-right shunt or valvular insufficiency), there is little room for further dilation as a means of augmenting cardiac output. The presence of lesions that result in increased afterload to the ventricle (e.g., aortic or pulmonic stenosis, coarctation of the aorta) decreases cardiac performance, thereby resulting in a depressed Frank-Starling relationship.

Systemic oxygen transport is calculated as the product of cardiac output and oxygen content of systemic blood. **Cardiac output** can be calculated as the product of heart rate and stroke volume. The primary determinants of stroke volume are the *afterload* (pressure work), *preload* (volume work), and *contractility* (intrinsic myocardial function). Abnormalities in heart rate can also compromise cardiac output; for example, tachyarrhythmias shorten the diastolic time interval for ventricular filling. Alterations in the oxygen-carrying capacity of blood (e.g., anemia or hypoxemia) also lead to a decrease in systemic oxygen transport and, if compensatory mechanisms are inadequate, can result in decreased delivery of substrate to tissues.

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (e.g., secondary to anemia) or increased oxygen demands (e.g., secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body's needs. This condition, **high-output failure**, results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal. It is also seen with large systemic arteriovenous fistulas (e.g., vein of Galen malformation). These conditions reduce peripheral vascular resistance and cardiac afterload and increase myocardial contractility. Heart failure results when the demand for cardiac output exceeds the ability of the heart to respond.

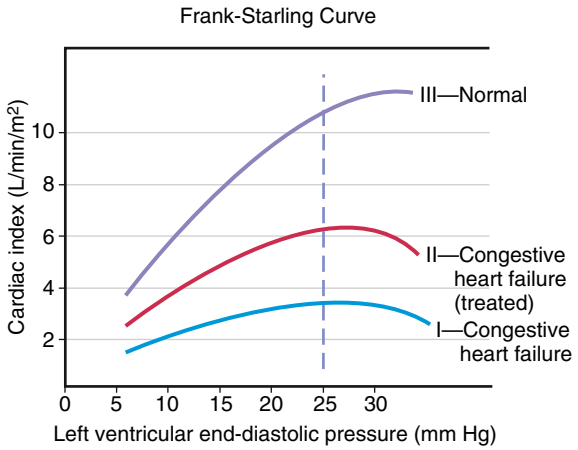

Fig. 491.1 The Frank-Starling relationship. As left ventricular end-diastolic (LVED) pressure increases, the cardiac index increases, even in the presence of congestive heart failure, until a critical level of LVED pressure is reached. Adding an inotropic agent (digoxin) shifts the curve from I to II. *(From Gersony WM, Steep CN. In: Dickerman JD, Lucey JF, eds. Smith's The Critically Ill Child: Diagnosis and Medical Management, 3rd ed. Philadelphia: Saunders; 1984.)*

Chronic severe high-output failure may eventually result in a decrease in myocardial performance as the metabolic requirements of the myocardium are not met.

Multiple systemic compensatory mechanisms are used by the body to adapt to chronic heart failure. Some are mediated at the molecular/cellular level, such as upregulation or downregulation of various metabolic pathway components leading to changes in efficiency of oxygen and other substrate utilizations. Others are mediated by neurohormones such as the renin-angiotensin system and the sympathoadrenal axis. One of the principal mechanisms for increasing cardiac output is an increase in sympathetic tone secondary to increased secretion of circulating epinephrine by the adrenals and increased release of norepinephrine at the neuromuscular junction. The *initial* beneficial effects of sympathetic stimulation include an increase in heart rate and myocardial contractility, mediated by these hormones' action on cardiac β-adrenergic receptors, increasing cardiac output. These hormones also cause vasoconstriction, mediated by their action on peripheral arterial α-adrenergic receptors. Some vascular beds may constrict more readily than others, so that blood flow is redistributed from the cutaneous, visceral, and renal beds to the heart and brain. Whereas these acute effects are beneficial, *chronically* increased sympathetic stimulation can have deleterious effects, including hypermetabolism, increased afterload, arrhythmogenesis, and increased myocardial oxygen requirements. Peripheral vasoconstriction can result in decreased renal, hepatic, and gastrointestinal tract function. Chronic exposure to circulating catecholamines leads to a decrease in the number of cardiac β-adrenergic receptors (downregulation) and also causes direct myocardial cell damage. Therapeutic agents for heart failure are directed at restoring balance to these neuroendocrine systems.

Based on these physiologic and clinical principles, heart failure has been described by different **classification** and **stage** definitions (Tables 491.1-491.3 and Fig. 491.2). These definitions help describe the degree of cardiac impairment and help direct therapy.

Table 491.1 Classification of Heart Failure Based on LVEF

HF CLASS ACCORDING TO LVEF (MUST HAVE SIGNS AND SYMPTOMS)	ACRONYM	LVEF, %
HF with reduced ejection fraction	HFrEF	≤40
HF with mildly reduced ejection fraction	HFmrEF	41–49
HF with preserved ejection fraction	HFpEF	≥50
HF with preserved ejection fraction, improved	HFpEF, improved	Prior <40, now ≥40

LVEF, Left ventricular ejection fraction.
From Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023: Table 2, p. 117.

Table 491.2 New York Heart Association (NYHA) Functional Classification (FC)

NYHA FC	FUNCTIONAL CAPACITY
I	No limitations. Can perform high level of activity without symptoms (for example, running, cycling, weightlifting).
II	Slight limitations. Tolerate lower or moderate level activities well, may have limitations with higher-level activities (for example, regular walking causes no symptoms, but a run may cause shortness of breath).
III	Significant limitations. Symptoms with low-level activities such as with daily activities such as walking and household chores.
IV	Symptoms at rest, dyspnea with any physical activity.

From Kellerman RD, Rakel DP, Heidelbaugh JJ, Lee EM, eds. *Conn's Current Therapy 2023.* Philadelphia: Elsevier; 2023: Table 3, p. 117.

ETIOLOGY OF HEART FAILURE

There are many causes of heart failure in the pediatric population, and the etiologies of heart failure are age-dependent (Table 491.4). Pediatric heart failure can occur because of ventricular systolic or diastolic dysfunction caused by an underlying cardiomyopathy. This may be the result of a primary cardiomyopathy from an underlying genetic mutation in cardiac proteins or secondary due to conditions including metabolic and neuromuscular diseases. Ischemic cardiomyopathy caused by congenital coronary anomalies or acquired disease, such as Kawasaki disease, can also result in heart failure. Inflammatory or infectious diseases of the myocardium (e.g., myocarditis) can present with a range of heart failure severity from mild symptoms of chest pain to severe disease with fulminant cardiogenic shock. Persistent atrial and ventricular arrhythmias, particularly tachyarrhythmias, may also result in ventricular dysfunction and heart failure. High-output heart failure can occur in the setting of severe anemia or large arteriovenous malformations.

Heart failure in children can also occur in the setting of underlying congenital heart disease with outflow tract obstructive lesions, shunt lesions with overcirculation of the pulmonary vascular system (e.g., ventricular septal defect), or ventricular volume overload caused by significant valve regurgitation. Heart failure in children can also occur because of valvar heart disease resulting in significant valve regurgitation that causes ventricular volume overload and ventricular dilation with eventual systolic dysfunction. Single ventricle heart disease, including hypoplastic left heart syndrome, has increased the risk of developing heart failure due to multiple mechanisms that influence appropriate blood flow through the single ventricle palliated circulation.

CLINICAL MANIFESTATIONS

The clinical manifestations of heart failure depend in part on the degree of the child's cardiac reserve. A critically ill infant or child who has exhausted the compensatory mechanisms to the point that cardiac output is no longer sufficient to meet the basal metabolic needs of the body may present in **cardiogenic shock**. Other patients may be comfortable when quiet but are incapable of increasing cardiac output in response to even mild activity without experiencing significant symptoms. Conversely, it may take rather vigorous exercise to compromise cardiac function in children who have less severe heart disease.

A thorough **history** is extremely important in making the diagnosis of heart failure and in evaluating the possible causes. Parents or caregivers who observe their child on a daily basis may not recognize subtle changes that have occurred over the course of days or weeks. Gradually worsening perfusion or increasing respiratory effort may not be recognized as an abnormal finding, or may be misattributed to other diagnoses such as asthma. Edema, which is generally absent in infants and young children, may be passed off as normal weight gain, and exercise intolerance as lack of interest in an activity. The history of a young infant should also focus on **feeding**. An infant with heart failure often takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely. Eliciting a history of fatigue in an older child requires detailed questions about activity level and its course over several months.

In children and adolescents, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, exercise intolerance, anorexia, nausea, vomiting, dyspnea, edema, wheezing, and cough. Many children, however, may have primarily abdominal symptoms (abdominal pain, nausea, vomiting, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal radiograph unexpectedly catches the lower end of an enlarged heart.

The **physical examination** for a child with suspected heart failure includes evaluation of vital signs and physical exam. Abnormal vital signs sometimes seen in pediatric heart failure include tachypnea, tachycardia, and desaturation caused by pulmonary edema. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and

Table 491. 3 Classification of HF According to the American Heart Association (AHA) and American College of Cardiology (ACC)

HEART FAILURE STAGE		AHA/ACC DESCRIPTION
Stage A	At risk	Patients without identified structural or functional cardiac abnormality or ventricular function abnormality but at high risk of developing HF because of the presence of a condition (hypertension) strongly associated with the development of HF. Examples: anthracycline exposure, known pathogenic sarcomeric gene variant including dystrophinopathies.
Stage B	Pre-HF	Patients with structural heart disease or ventricular function abnormality that is strongly associated with the development of HF but without HF signs or symptoms, past or present. Examples: asymptomatic patient with CHD status postsurgical correction with residual lesion, isolated left ventricle noncompaction, elevated BNP or troponin if exposed to cardiotoxins.
Stage C	HF	Patients with current or prior symptoms of HF associated with underlying structural heart disease or ventricular function abnormality (elevated filling pressure, systolic dysfunction). Examples: acute myocarditis, dilated cardiomyopathy, mitral or aortic regurgitation.
Stage D	Advanced HF	Patients with advanced structural heart disease and refractory symptoms of HF requiring specialized interventions. Example: Inotropic dependency patient in end stage of dilated cardiomyopathy: may require VAD or transplant.

BNP, B-type natriuretic protein; CHD, congenital heart defect; VAD, ventricular assist devices; HF, heart failure
Modified from Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American college of cardiology/American heart association task force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure). *J Am Coll Cardiol.* 2001;38:2101–13.

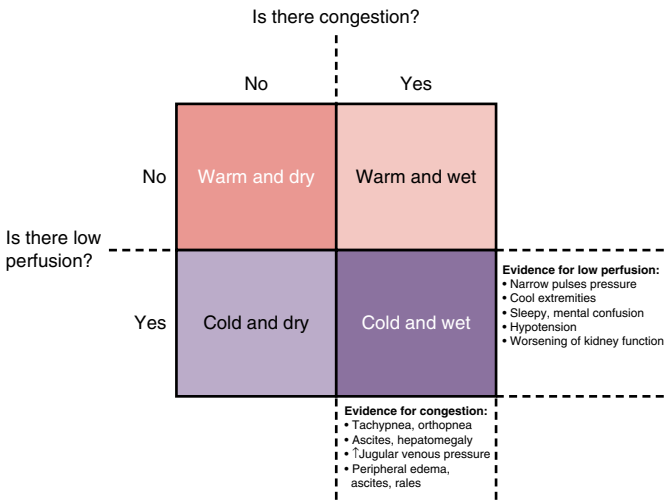

Fig. 491.2 Clinical assessment in acute decompensated heart failure should answer the two questions suggested by this diagram: First, does the patient present with significant congestion? Second, does the patient present with significant underperfusion? Using this construct, patients will segregate into one of four categories in accordance with clinical findings. Typically, patients move in a clockwise fashion through these categories, first becoming congested (warm and wet) and then vasoconstricted to maintain blood pressure (cold and wet). Once vasoactive support and diuresis are achieved, movement is generally counterclockwise, from cold and wet, to warm and wet, and then warm and dry. However, some patients will remain underperfused despite restoration of normovolemia, representing the cold and dry group, for whom mechanical support may be needed. *(Modified from Kantor PF, Mertens LL. Clinical practice: heart failure in children. Part I: clinical evaluation, diagnostic testing, and initial medical management. Eur J Pediatr. 2010;169[3]:269–279.)*

basilar rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted based on a hyperactive precordium, ventricular heave, or displaced apical impulse. A **gallop rhythm** is common; when ventricular dilation is advanced, the **holosystolic murmur** of mitral or tricuspid valve regurgitation may be heard. **Pulsus alternans** is an ominous physical exam finding usually seeing in a state of low stroke volume with variable cardiac output with each ventricular contraction. Impaired systemic perfusion with poor capillary refill or decreased pulses is a concerning sign for cardiogenic shock.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress or gastrointestinal diseases. Prominent manifestations of heart failure include tachypnea, feeding difficulties, vomiting, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Hepatomegaly usually occurs, and cardiomegaly is invariably present. Despite pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged liver is a more reliable sign.

DIAGNOSIS

Chest radiograph (CXR) may be helpful in pediatric heart failure. It can assess the cardiac silhouette for cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. Infants and children with large left-to-right shunts have exaggeration of the pulmonary arterial vessels to the periphery of the lung fields, whereas patients with cardiomyopathy may have a relatively normal pulmonary vascular bed early in the course of disease. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are seen only with more severe degrees of heart failure. Pleural effusions may also be present. Cardiac enlargement as a marker of heart failure may be noted on a chest radiography performed to evaluate for a possible pulmonary infection, bronchiolitis, or asthma.

Electrocardiography (ECG) may be helpful in assessing the cause of heart failure but does not establish the diagnosis. In cardiomyopathies, exaggerated left or right ventricular voltages may be suggestive of underlying cardiomyopathy, and ischemic changes may correlate with other noninvasive parameters of ventricular function. Low-voltage QRS morphologic characteristics with ST-T–wave abnormalities may also suggest myocardial inflammatory disease (myocarditis) but can be seen with pericarditis as well. ECG is the best tool for evaluating rhythm disorders as a potential cause of heart failure, especially tachyarrhythmias. Ambulatory ECG monitoring can evaluate for occult arrhythmias that may be present in heart failure.

Echocardiography is the standard technique for assessing ventricular function (Fig. 491.3). Ventricular function can be quantitated simply and reliably with commonly used parameters such as fractional shortening (a single-dimensional variable) and an ejection fraction. The *fractional shortening* is determined as the difference between

Table 491.4 Etiology of Heart Failure

FETAL
Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia)
Supraventricular tachycardia
Ventricular tachycardia
Complete heart block
Severe Ebstein anomaly or other severe right-sided lesions
Myocarditis
PREMATURE NEONATE
Fluid overload
Patent ductus arteriosus
Ventricular septal defect
Cor pulmonale (bronchopulmonary dysplasia)
Hypertension
Myocarditis
Genetic/metabolic cardiomyopathy
FULL-TERM NEONATE
Asphyxial cardiomyopathy
Arteriovenous malformation (vein of Galen, hepatic)
Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome)
Large mixing cardiac defects (single ventricle, truncus arteriosus)
Myocarditis
Genetic/metabolic cardiomyopathy
Pheochromocytoma
Stress cardiomyopathy (Takotsubo)
Substance misuse
INFANT/TODDLER
Left-to-right cardiac shunts (ventricular septal defect)
Hemangioma (arteriovenous malformation)
Anomalous left coronary artery
Genetic/metabolic cardiomyopathy
Acute hypertension (hemolytic-uremic syndrome)
Supraventricular tachycardia
Kawasaki disease
Myocarditis
CHILD/ADOLESCENT
Congenital heart disease (various forms, including single ventricle heart disease)
Rheumatic fever
Acute hypertension (glomerulonephritis)
Myocarditis
Thyrotoxicosis
Hemochromatosis-hemosiderosis
Cancer therapy (radiation, doxorubicin)
Sickle cell anemia
Endocarditis
Cor pulmonale (cystic fibrosis)
Genetic/metabolic cardiomyopathy (hypertrophic, dilated)

end-systolic and end-diastolic diameter divided by end-diastolic diameter. Normal fractional shortening is between approximately 28% and 42%. The *ejection fraction* uses two-dimensional data to calculate a three-dimensional volume; the normal range is 55–65%. In children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short-axis view will not be accurate. Doppler studies can also be used to estimate cardiac output. Doppler assessment of transmitral inflow and tissue characterization can also be used as a noninvasive assessment of diastolic function.

Cardiac magnetic resonance imaging (CMR) is also useful in quantifying left and right ventricular function, volume, and mass along with coronary artery anatomy. If valvular regurgitation is present, CMR can quantify the regurgitant fraction. CMR can also provide details about tissue characterization such as fibrosis and inflammation, which is helpful for assessing conditions such as myocarditis.

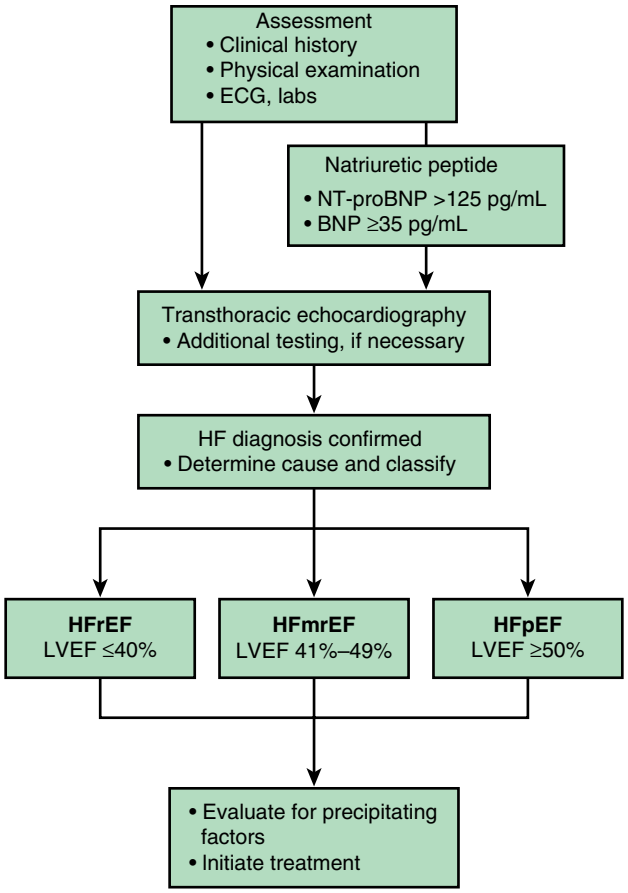

Fig. 491.3 Diagnostic algorithm for HF- and EF-based classification BNP, B-type natriuretic peptide; ECG, electrocardiogram; EF, ejection fraction; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LV, left ventricular; NT-proBNP, N-terminal pro-B type natriuretic peptide. *(From Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Amer Coll Cardiol. 2022;79[17]:1757–1780, Fig. 4.)*

Cardiac catheterization is an invasive test that can be helpful for assessing heart failure by evaluating intracardiac hemodynamics and shunt lesions. Angiography can be performed to evaluate for structural heart defects. Endomyocardial biopsy may sometimes be performed as part of an evaluation of myocarditis.

Laboratory testing is important for evaluating end-organ function and systemic perfusion. This includes evaluating renal function, liver function, lactate levels, and electrolytes. Heart failure may result in hyponatremia caused by compensatory activation of the renin-angiotensin-aldosterone pathway with renal water retention, which may be compounded by further salt wasting due to chronic diuretic treatment. When heart failure is severe, respiratory acidosis or metabolic acidosis, or both, may be present. The cardiac serum **biomarker B-type (brain) natriuretic peptide (BNP)** (or N-terminal pro-BNP) is a cardiac neurohormone released in response to increased ventricular wall tension that is elevated in patients with heart failure. In children with heart failure, BNP may be elevated as a result of systolic dysfunction (e.g., cardiomyopathy) and in children with volume overload (e.g., left-to-right shunts such as ventricular septal defect). Table 491.5 lists other causes of an elevated BNP.

TREATMENT

The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiac anomaly amenable to surgery, medical treatment of the heart failure is indicated to prepare the patient for surgery. With the current excellent outcomes of primary surgical repair of congenital heart defects, even in the neonatal period,

Table 491.5 Causes of Elevated Concentrations of Natriuretic Peptides

CARDIAC
Heart failure (HFpEF, HFrEF)
Acute coronary symptoms
Pulmonary embolism
Myocarditis
Left ventricular hypertrophy
Hypertrophic or restrictive cardiomyopathy
Valvular heart disease
Congenital heart disease
Atrial and ventricular tachyarrhythmias
Heart contusion
Cardioversion ICD shock
Surgical procedures involving the heart
Pulmonary hypertension
Toxic injury (chemotherapy)
NONCARDIAC
Ischemic stroke
Subarachnoid hemorrhage
Renal dysfunction
Liver dysfunction (mainly liver cirrhosis with ascites)
Paraneoplastic syndrome
Chronic obstructive pulmonary disease
Severe infections (including pneumonia and sepsis)
Severe burns
Anemia
Severe metabolic and hormone abnormalities (e.g., thyrotoxicosis, diabetic ketosis)

HFpEF, Heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator.

Adapted from McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in *Eur Heart J*. 2021 Oct 14]. *Eur Heart J*. 2021;42(36):3599–3726, Table 7.

few children require aggressive heart failure management to grow big enough for surgery. In contrast, if the cause of heart failure is cardiomyopathy, medical management provides temporary relief from symptoms and may allow the patient to recover if the insult is reversible (e.g., myocarditis). If the lesion is not reversible, heart failure management usually allows the child to return to normal activities for some period and to delay, sometimes for months or years, the need for heart transplantation.

General Measures

Heart failure management focuses on maintaining adequate cardiac output to allow for appropriate end-organ function while reducing volume overload and venous or pulmonary congestion. Encouraging regular physical activity is important for preventing acquired cardiovascular comorbidities, but it is important that the child be allowed to rest as needed and monitor for cardiac symptoms. Formal **cardiopulmonary exercise** testing can be used to assess the patient's ability to perform exercise in a controlled environment and is useful for providing exercise recommendations. Malnutrition is common in patients with heart failure because of gastrointestinal symptoms related to mesenteric venous congestion, and patients often require supplemental nutrition either with caloric fortification and/or nasogastric supplementation. For patients with pulmonary edema, positive pressure ventilation (PPV) may be required along with other drug therapies. For those in low-output heart failure, PPV can significantly reduce total body oxygen consumption by eliminating the work of breathing and help to reverse metabolic acidosis. Reverse remodeling agents, including β blockers, angiotensin-blockers, combination angiotensin receptor/neprilysin inhibitors, and aldosterone antagonists, can provide long-term myocardial reverse remodeling. Appropriate blood pressure control is important to reduce afterload and stress on the myocardium. In patients with advanced heart failure and/or cardiogenic shock, providing adequate cardiac output to meet the metabolic demands and provide adequate end-organ perfusion may require inotropic agents and, potentially, mechanical circulation support (Table 491.6).

Diet

Infants with heart failure usually fail to thrive because of a combination of increased metabolic demands and decreased caloric intake. Increasing daily calories is an important aspect of their management. Increasing the number of calories per ounce of infant formula (or supplementing breastfeeding) may be beneficial. Many infants do not tolerate an increase beyond 24 calories/oz because of diarrhea or because these formulas provide too large a solute load for compromised kidneys.

Severely ill infants and children may lack sufficient strength for effective sucking because of extreme fatigue, rapid respirations, and generalized weakness. In these circumstances, nasogastric feedings may be helpful. In many patients with cardiac enlargement, **gastroesophageal reflux** is a major problem. The use of continuous drip nasogastric feedings at night, administered by pump, may improve caloric intake while decreasing problems with reflux. Continued **malnutrition** may be an important factor in the decision to undertake earlier surgical intervention in patients who have an operable congenital heart lesion or to proceed with mechanical circulatory support and/or listing for transplantation in patients with cardiomyopathy. *Iron supplementation should be initiated in the presence of iron deficiency even in the absence of anemia.*

The use of low-sodium formulas in the routine management of infants with heart failure is not recommended because these preparations are often poorly tolerated and may exacerbate diuretic-induced hyponatremia. Human breast milk is the ideal low-sodium nutritional source. The use of more potent diuretic agents allows more palatable standard formulas to be used for nutrition while controlling salt and water balance by chronic diuretic administration. Most older children can be managed with generally heart-healthy diets that have low fat and sugar content, although caloric supplementation may be needed if there is significant malnutrition.

Diuretics

Diuretics are an important component of heart failure management by reducing volume overload and congestion. Diuretics interfere with reabsorption of water and sodium by the kidneys, which results in a reduction in circulating blood volume and thereby reduces pulmonary fluid overload and ventricular filling pressure. Diuretics are usually the first mode of therapy initiated in patients with congestive heart failure.

Loop diuretics, including Furosemide and bumetanide, are the most commonly used diuretics in pediatric patients with heart failure. It inhibits the reabsorption of sodium and chloride in the distal tubules and the loop of Henle. Patients requiring acute diuresis should be given intravenous (IV) furosemide at an initial dose of 1-2 mg/kg, which usually results in rapid diuresis and prompt improvement in clinical status, particularly if symptoms of pulmonary congestion are present. Chronic furosemide therapy is then prescribed at a dose of 1-4 mg/kg/24 hr given between 1 and 4 times a day. Careful monitoring of electrolytes is necessary with long-term furosemide therapy because of the potential for significant loss of potassium. Potassium chloride supplementation is usually required unless the potassium-sparing diuretics are given concomitantly. Chronic administration of furosemide may cause contraction of the extracellular fluid compartment and result in "contraction alkalosis" (see Chapter 73.7). Diuretic-induced hyponatremia may become difficult to manage in patients with severe heart failure.

Thiazide diuretics, including chlorothiazide, are also used for diuresis in children with heart failure. It is less immediate in action and less potent than furosemide, and it affects the reabsorption of electrolytes in the renal tubules only. The usual dose is 10-40 mg/kg/24 hr in two divided doses. Potassium supplementation is often required if chlorothiazide is used alone. **Sodium glucose cotransporter 2 (SGLT2) inhibitors** (dapagliflozin, empagliflozin) also produce a natriuresis and have other beneficial direct cardiac effects and have been recommended for some etiologies of heart failure.

Table 491.6 Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE*
DIGOXIN	
Digitalization (1/2 initially, followed by 1/4 q12h × 2)	Premature: 20 μg/kg Full-term neonate (up to 1 mo): 20-30 μg/kg Infant or child: 25-40 μg/kg Adolescent or adult: 0.5-1 mg in divided doses *Note:* These doses are PO; IV dose is 75% of PO dose
Maintenance digoxin†	5-10 μg/kg/day, divided q12h *Note:* These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 μg/kg/min
Dopamine	2-20 μg/kg/min
Epinephrine	0.01-1.0 μg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 μg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Premature: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h Infant: start at 0.15-0.3 mg/kg/dose; 1.5-6 mg/kg/day, divided q6-12h Child: start at 0.3-0.5 mg/kg/dose; 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 μg/kg/min start; increase to 20 μg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 μg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose: 0.1 mg/kg/day (maximum: 6.25 mg) divided bid (may use tid in infants), increase gradually (usually 2-wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximum dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, non–extended-release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2-wk intervals) to maximum dose of 1-2 mg/kg/day PO, extended-release form (Toprol-XL): given once daily; adult initial dose: 25 mg/day, maximum: 200 mg/day

*Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.
†Maintenance digitalis therapy is started approximately 12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in two and given at 12-hr intervals. The oral maintenance dose is usually 20–25% higher than when digoxin is used parenterally. The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.
IV, Intravenous; PO, oral; bid, twice daily, tid, 3 times daily; qid, 4 times daily; qd, every day.

Cardiac Reverse Remodeling

Angiotensin Antagonists

The renin-angiotensin-aldosterone pathway becomes active as a compensatory response to heart failure, but these compensatory effects can result in increased afterload and adverse remodeling of the myocardium, including development of cardiac fibrosis. Angiotensin antagonists, including angiotensin-converting enzyme inhibitors (ACEIs) and aldosterone II receptor blockers (ARBs), reduce ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. Afterload reducers may be useful in children with heart failure secondary to cardiomyopathy and in patients with severe mitral or aortic insufficiency. They may also be effective in patients with heart failure caused by left-to-right shunts. ACEIs and ARBs may have additional beneficial effects on cardiac remodeling independent of their influence on afterload by directly influencing adverse cardiac intracellular signaling pathways and decreasing the formation of myocardial fibrosis. In adult patients with dilated cardiomyopathy, the addition of an ACEI to standard medical therapy reduces both morbidity and mortality.

The orally active ACEIs **captopril**, **enalapril,** and **lisinopril** produce arterial dilation by blocking the production of angiotensin II, thereby resulting in significant afterload reduction. Venodilation and consequent preload reduction also have been reported. In addition, these agents interfere with aldosterone production and therefore also help control salt and water retention. ACEIs have additional beneficial effects on cardiac structure and function that may be independent of

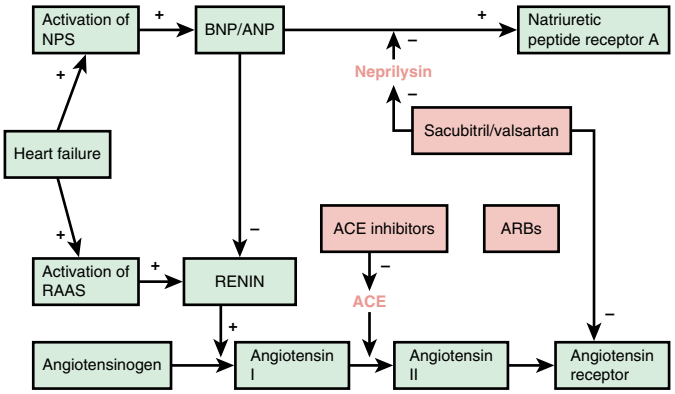

Fig. 491.4 Systems activated in heart failure and pathways blocked by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and neprilysin inhibitors (sympathetic nervous system activation pathway is not shown in the figure). ANP, Atrial natriuretic peptide; BNP, B-type natriuretic peptide; NPS, natriuretic peptide system; RAAS, renin angiotensin aldosterone system. *(From Arya A, Azad S, Sitaraman R. Angiotensin receptor and neprilysin inhibitor: a new drug in pediatric cardiologist's armamentarium. Ann Pediatr Cardiol. 2020;13[4]:334–336, Fig. 1.)*

Table 491.7 Valsartan/Sacubitril Recommended Dose* (Twice Daily)

	STARTING	SECOND	FINAL
Pediatric patients <40 kg** (mg/kg)	1.6	2.3	3.1
Pediatric patients at least 40 kg, <50 kg (mg)	24/26	49/51	72/78#
Pediatric patients at least 50 kg (mg)	49/51	72/78#	97/103

*Available as 24/26, 49/51, and 97/103 mg tablets, where the first drug is sacubitril and the second drug is valsartan.
#Doses of 72/78 mg can be achieved using three 24/26 mg tablets. Titration: titrate dose every 2 wk and target final dose.
**An oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.
From Arya A, Azad S, Sitaraman R. Angiotensin receptor and neprilysin inhibitor: a new drug in pediatric cardiologist's armamentarium. *Ann Pediatr Cardiol.* 2020;13(4):334–336, Table 1.

their effect on afterload. Adverse reactions to ACEIs include hypotension and its sequelae (weakness, dizziness, syncope) and hyperkalemia. A maculopapular pruritic rash is encountered in a small number of patients, but the drug may be continued because the rash often disappears spontaneously with time. Neutropenia, renal toxicity, and chronic cough also occur. Angioedema is a rare side effect of ACEIs and is related to inhibiting breakdown of bradykinin. If patients have had side effects related to bradykinin effect from ACEIs, including chronic cough, ARBs may be an alternative therapy and include **losartan** and **valsartan.**

An angiotensin receptor combined with neprilysin inhibition (ARNI) (valsartan/sacubitril) is approved for children 1-18 years of age with New York Heart Association class II-IV and a left ventricular ejection fraction ≤40%. The mechanism of action is noted in Figure 491.4 and the dosing in Table 491.7.

Aldosterone Antagonists

Spironolactone and **eplerenone** inhibit aldosterone and act both as a reverse remodeling agent and a weak diuretic. They also enhance potassium retention, often eliminating the need for oral potassium supplementation in patients receiving diuretics. Aldosterone antagonists blunt the adverse cardiac remodeling effects and may reduce cardiac fibrosis that results in heart failure. Spironolactone is usually given orally in two divided doses of 2 mg/kg/24 hr. Adults with heart failure have improved survival when an aldosterone inhibitor is included in the diuretic regimen, likely through multiple effects, including a favorable effect on cardiac fibrosis. Eplerenone is an alternative to spironolactone and does not have the side effect of gynecomastia.

β Blockers

Studies in adults with dilated cardiomyopathy show that β-adrenergic blocking agents, introduced gradually as part of a comprehensive heart failure treatment program, improve exercise tolerance, decrease hospitalizations, and reduce overall mortality. The agents most often used are **carvedilol**, with both α- and β-adrenergic receptor–blocking and free radical–scavenging effects, and **metoprolol**, a β_1-adrenergic receptor–selective antagonist. β Blockers are used for the chronic treatment of patients with heart failure and should not be administered when patients are still in the acute phase of heart failure (i.e., receiving IV adrenergic agonist infusions). Although highly efficacious in adults, clinical studies in children have shown mixed results, potentially from the significant heterogeneity of the populations being studied and differences in the types of β-blocking agents.

Although ACEIs/ARBs along with β-adrenergic–blocking agents and aldosterone antagonists have been shown in multiple prospective, randomized, controlled trials in adults to improve symptoms and mortality in adult heart failure patients, it is unclear if these medications improve the natural history of heart failure in children. Nonetheless, these medications are commonly used for the treatment of heart failure and are recommended by consensus guidelines from the ISHLT and Canadian Cardiovascular Society.

Afterload Reduction

Afterload reduction is an important component of heart failure management to reduce workload on the myocardium. Oral afterload-reducing agents, including ACEIs and ARBs, are often used for both cardiac reverse remodeling and afterload reduction benefits. If renal insufficiency is present, alternative oral afterload-reducing agents may be considered, including calcium channel blockers such as **amlodipine**, although they have potential side effects including peripheral edema and gingival hyperplasia.

Intravenously administered afterload-reducing agents, including **milrinone** (see later section on "Phosphodiesterase Inhibitors"), **nicardipine**, and **nitroprusside**, should be initiated only in a closely monitored clinical care setting. Nitroprusside's short IV half-life makes it ideal for titrating the dose in critically ill patients. Peripheral arterial vasodilation and afterload reduction are the major effects, but venodilation causing a decrease in venous return to the heart may also be beneficial. Blood pressure must be continuously monitored because sudden hypotension can occur. Consequently, nitroprusside is contraindicated in patients with preexisting hypotension. Because the drug is metabolized, small amounts of circulating cyanide are produced and detoxified in the liver to thiocyanate, which is excreted in urine. When high doses of nitroprusside are administered for several days, toxic symptoms related to *thiocyanate poisoning* may occur (fatigue, nausea, disorientation, acidosis, and muscular spasm). If nitroprusside use is prolonged, blood thiocyanate levels should be monitored.

Phosphodiesterase Inhibitors

Milrinone is useful in treating patients with low cardiac output who are refractory to standard therapy. It has been shown to be highly effective in managing the low-output state present in children after open heart surgery. It works by inhibiting phosphodiesterase, which prevents the degradation of intracellular cyclic adenosine monophosphate. Milrinone has both positive inotropic effects on the heart and peripheral vasodilatory effects and has generally been used as an adjunct to dopamine or dobutamine therapy in the intensive care unit. It is given by IV infusion at 0.25-1 μg/kg/min. A major side effect is **hypotension** secondary to peripheral vasodilation. The hypotension can generally be managed by the administration of IV fluids to restore adequate intravascular volume. Because of renal clearance of milrinone, caution must be used in the setting of renal insufficiency. Long-term milrinone

is often used to support patients while listed for heart transplantation, and in select patients can be used in the outpatient setting.

α- and β-Adrenergic Agonists

The α- and β-adrenergic receptor agonists may be needed for advanced heart failure with impaired cardiac output and are usually administered in an intensive care setting, where the dose can be carefully titrated to hemodynamic response. Continuous determinations of arterial blood pressure and heart rate are performed; measuring serial mixed venous oxygen saturations or cardiac output directly with a pulmonary thermodilution (Swan-Ganz) catheter may be helpful in assessing drug efficacy, although this technique is used much less in children than in adults. These agents increase myocardial oxygen consumption and are associated with increased arrhythmogenic burden and have been shown to increase morbidity and mortality in adults with heart failure; thus they are usually avoided as a long-term therapy.

Dopamine is a predominantly β-adrenergic receptor agonist, but it has α-adrenergic effects at higher doses. Dopamine has less chronotropic and arrhythmogenic effect than the pure β-agonist isoproterenol. At a dose of 2-10 μg/kg/min, dopamine results in increased contractility with little peripheral vasoconstrictive effect. If the dose is increased beyond 15 μg/kg/min, however, its peripheral α-adrenergic effects may result in vasoconstriction.

Dobutamine, a derivative of dopamine, is also useful in treating low cardiac output. It has direct inotropic effects and causes a moderate reduction in peripheral vascular resistance. Dobutamine can be used alone or as an adjunct to dopamine therapy to avoid the vasoconstrictive effects of higher-dose dopamine. Dobutamine is also less likely to cause cardiac rhythm disturbances.

Epinephrine is a mixed α- and β-adrenergic receptor agonist that is usually reserved for patients with cardiogenic shock and low arterial blood pressure. Although epinephrine can raise blood pressure effectively, it also increases systemic vascular resistance, and therefore increases the afterload against which the heart has to work and is associated with an increased risk of arrhythmia. Additionally, epinephrine is proarrhythmic and can result in direct cardiac toxicity, including myocardial necrosis and apoptosis.

Digitalis Glycosides

Digoxin, once the mainstay of heart failure management in both children and adults, is currently used less frequently as a result of the introduction of other therapies and the recognition of its potential toxicities. Some cardiologists will use digitalis as an adjunct to ACEIs and diuretics in patients with symptomatic heart failure, whereas others have stopped using it altogether. Despite multiple clinical studies, predominantly in adults, the controversy over digitalis remains. Some data suggest a beneficial effect of digoxin on reducing death among infants with single ventricle heart disease.

Digoxin is the digitalis glycoside used most often in pediatric patients. It has a half-life of 36 hours and is absorbed well by the gastrointestinal tract (60–85%), even in infants. An initial effect is seen as early as 30 minutes after administration, and the peak effect for oral digoxin occurs at 2-6 hours. When the drug is administered intravenously, the initial effect is seen in 15-30 minutes, and the peak effect occurs at 1-4 hours. The kidney eliminates digoxin, so dosing must be adjusted according to the patient's renal function. The half-life of digoxin may be up to 6 days in patients with anuria because slower hepatic excretion pathways are used in these patients.

Rapid digitalization of infants and children may be carried out intravenously. This should be done with caution in patients with severe heart failure. The dose depends on the patient's age (see Table 491.6). The recommended digitalization schedule is to give half the total digitalizing dose immediately and the succeeding two one-quarter doses at 12-hours intervals later. The ECG must be closely monitored and rhythm strips obtained before each of the three digitalizing doses. Digoxin should be discontinued if a new rhythm disturbance is noted. Prolongation of the P-R interval is not necessarily an indication to withhold digitalis, but a delay in administering the next dose or a reduction in the dosage should be considered, depending on the patient's clinical status. Minor ST segment or T-wave changes are frequently noted with digitalis administration and should not affect the digitalization regimen. Baseline serum electrolyte levels should be measured before and after digitalization. **Hypokalemia** and **hypercalcemia** exacerbate digitalis toxicity. Because hypokalemia is relatively common in patients receiving diuretics, potassium levels should be monitored closely in those receiving a potassium-wasting diuretic in combination with digitalis. In patients with active myocarditis, some cardiologists recommend avoiding digitalis altogether, and if used, maintenance digitalis should be started at half the normal dose without digitalization because of the increased risk of arrhythmia in these patients.

Patients who are not critically ill may be given digitalis initially by the oral route, and in most instances, digitalization is completed within 24 hours. When slow digitalization is desirable, for example, in the immediate postoperative period, initiation of a maintenance digoxin schedule without a previous loading dose achieves full digitalization in 7-10 days.

Measurement of serum digoxin levels is useful in the following circumstances: (1) when an unknown amount of digoxin has been administered or ingested accidently, (2) when renal function is impaired or if drug interactions are possible, (3) when questions regarding compliance are raised, and (4) when a toxic response is suspected. In suspected toxicity, elevated serum digoxin levels are not in themselves diagnostic of toxicity but must be interpreted as an adjunct to other clinical and electrocardiographic findings (rhythm and conduction disturbances). Hypokalemia, hypomagnesemia, hypercalcemia, cardiac inflammation secondary to myocarditis, and prematurity may all potentiate digitalis toxicity. A cardiac arrhythmia that develops in a child who is taking digitalis may also be related to the primary cardiac disease rather than the drug; however, any arrhythmia occurring after the institution of digitalis therapy must be considered to be drug related until proven otherwise. Many drugs interact with digoxin and may increase levels or risk of toxicity, so care should be taken when a patient receiving digoxin is being considered for any additional pharmacologic therapy.

Additional Therapies

Several medications that have shown promise in the treatment of adult patients with heart failure are being studied in pediatric patients. For chronic heart failure, **ivabradine** has been studied in patients with elevated heart rates despite optimized β blocker use. Ivabradine is a selective inhibitor of the I_f current in the sinus node and lowers heart rates without decreasing myocardial contractility. The use of ivabradine was associated with improved outcomes in adults with heart failure, and a recent study of children with heart failure caused by dilated cardiomyopathy demonstrated improved left ventricular systolic function and clinical status.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, which blocks reabsorption of glucose in the proximal renal tubule, are the newest class of adult heart failure medications and, though developed as a treatment for diabetes, have shown dramatic improvement in cardiac mortality and morbidity in adults with heart failure with reduced ejection fraction. Given the mechanism of action, which includes glucosuria, there is a risk for urinary tract infection and yeast infection. Additional possible side effects include acute kidney injury and bone fracture as well as development of diabetic ketoacidosis in patients with diabetes. Further studies are needed to determine what role, if any, these medications will have in the treatment of pediatric heart failure.

ELECTROPHYSIOLOGIC APPROACHES TO HEART FAILURE MANAGEMENT

Significant improvements in symptomatology and functional capacity have been achieved in select adult patients with cardiomyopathy using **biventricular resynchronization pacing**. This technique improves cardiac output by restoring normal synchrony between right and left ventricular contraction, which is often lost in patients with dilated cardiomyopathy (these patients usually manifest a left bundle branch block on ECG). There is growing experience with resynchronization pacing in children, but it remains uncertain which population of patients with heart failure benefit from this therapy.

Arrhythmias are a leading cause of sudden death in patients with severe cardiomyopathy (both dilated and hypertrophic). Although antiarrhythmic medications can sometimes reduce this risk, for patients at particularly high risk (e.g., those with a condition known to be associated with a high risk of ventricular arrhythmia or those who have already

Table 491.8 Treatment of Cardiogenic Shock*

	DETERMINANTS OF STROKE VOLUME		
	Preload	**Contractility**	**Afterload**
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O_2 saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACEIs

*The goal is to improve peripheral perfusion by increasing cardiac output, where cardiac output = heart rate × stroke volume.
ACEIs, Angiotensin-converting enzyme inhibitors; BP, blood pressure; CO, cardiac output (measured with a thermodilution catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O_2 saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilution catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

experienced a "missed sudden death" episode), use of an **implantable cardioverter-defibrillator** can be lifesaving (see Chapter 485).

491.1 Cardiogenic Shock

Joseph W. Rossano and Danielle S. Burstein

Cardiogenic shock may be caused by (1) severe cardiac dysfunction before or after cardiac surgery, (2) septicemia, (3) severe burns, (4) anaphylaxis, (5) cardiomyopathy, (6) myocarditis, (7) myocardial infarction or stunning, and (8) acute central nervous system (CNS) disorders. It is characterized by low cardiac output and results in inadequate tissue perfusion (see Chapter 85).

Treatment is aimed at restoring adequate cardiac output to prevent the untoward effects of prolonged ischemia on vital organs, as well as management of the underlying cause. Under normal physiologic conditions, cardiac output is increased as a result of sympathetic stimulation, which increases both contractility and heart rate. If contractility is depressed, cardiac output may be improved by increasing the heart rate, increasing ventricular filling pressure (preload) through the Frank-Starling mechanism, or decreasing systemic vascular resistance (afterload). Optimal filling pressure is variable and depends on a number of extracardiac factors, including ventilatory support and intraabdominal pressure. The increased pressure necessary to fill a relatively noncompliant ventricle should also be considered, particularly after open heart surgery or in patients with restrictive or hypertrophic cardiomyopathies. If carefully administered incremental fluid does not result in improved cardiac output, abnormal myocardial contractility or an abnormally high afterload, or both, must be implicated as the cause of the low cardiac output. Although an increase in heart rate *may* improve cardiac output, an excessive increase in heart rate may reduce cardiac output because of decreased time for diastolic filling. Additionally, high heart rates will increase myocardial oxygen demand, which may be counterproductive in a state of limited tissue oxygen supply.

Myocardial contractility usually improves when treatment of the basic cause of shock is instituted, hypoxia is eliminated, and acidosis is corrected. β-Adrenergic agonists such as dopamine, epinephrine, and dobutamine improve cardiac contractility, increase heart rate, and ultimately increase cardiac output. However, some of these agents also have α-adrenergic effects, which cause peripheral vasoconstriction and increase afterload, so careful consideration of the balance of these effects in an individual patient is important. The use of cardiac glycosides and β blockers to treat acute low-cardiac-output states should be avoided.

Patients in cardiogenic shock may have a marked increase in systemic vascular resistance (SVR) resulting in high afterload and poor peripheral perfusion. If the increased SVR is persistent and the administration of positive inotropic agents alone does not improve tissue perfusion, the use of afterload-reducing agents may be appropriate, such as nitroprusside or milrinone in combination with a β-adrenergic agonist. Milrinone, a phosphodiesterase inhibitor (see earlier), is also a positive inotropic agent, and combined with a β-adrenergic agonist, it works synergistically to increase levels of myocardial cyclic adenosine monophosphate.

Sequential evaluation and management of cardiovascular shock are mandatory (see Chapter 85). Table 491.8 outlines the general treatment principles for acute cardiac circulatory failure under most circumstances. In addition to cardiac-specific medications, other treatments aimed at improving oxygen capacity (e.g., blood transfusion for patients with anemia) and decreasing oxygen demand (e.g., intubation, mechanical ventilation, sedation, antipyretics) can be beneficial. Treatment of infants and children with low cardiac output after cardiac surgery also depends on the nature of the operative procedure, any intraoperative complications, and the physiology of the circulation after repair or palliation (see Chapter 483). If cardiogenic shock does not respond rapidly to medical therapy, consideration of mechanical support is warranted.

MECHANICAL CIRCULATORY SUPPORT

Extracorporeal membrane oxygenation (ECMO), which can provide total cardiopulmonary support, is the most common *short-term* modality to support circulatory failure in children. In experienced centers, children can be placed on ECMO rapidly, and therefore the modality can be used in multiple settings, including low cardiac output syndrome (low-output heart failure) after cardiac surgery, rapidly deteriorating hemodynamics in several scenarios (e.g., myocarditis), and as resuscitation from refractory cardiac arrest. The modality is ideal for short-term support when the underlying disease requiring ECMO is expected to resolve within days to weeks. For multiple reasons, including the relatively high complication rate and decreased mobility of many patients on ECMO, it is not an ideal support modality for long-term myocardial support.

Given the limitations of ECMO, there is a need to develop long-term support options for children with refractory heart failure. **Ventricular assist devices (VADs)** include both short-term and long-term mechanical circulatory support and can be deployed either percutaneously or surgically. In children, most of these devices are used with the intention of subsequently performing a heart transplantation, although the devices can be removed if myocardial function recovers. This is in contrast to adult patients, many of whom are placed on these devices with no plan for heart transplantation, the so-called *destination therapy.* Successfully managing patients on VAD support requires a dedicated multidisciplinary team.

For infants and small children, the most commonly used VADs are paracorporeal devices, including paracorporeal pulsatile-flow VADs (e.g., Berlin Heart EXCOR) and paracorporeal continuous-flow VADs (e.g., Pedimag). These devices can be used for left, right, or biventricular support. They are classified as a paracorporeal device because the pump sits outside the body. In older children and adolescents, intracorporeal continuous flow devices (e.g., HeartMate3) are preferred. These VADs are completely internalized except for a drive line that connects to the power source (Fig. 491.5). These VADs have fewer complications and can provide long-term durable support outside the hospital. These devices are often used in older children and adolescents, with many of these patients discharged home on VAD support. Other types of devices, including **temporary percutaneous VAD** (e.g., Impella) for short-term support and the **total artificial heart** for long-term support, have also been used in children.

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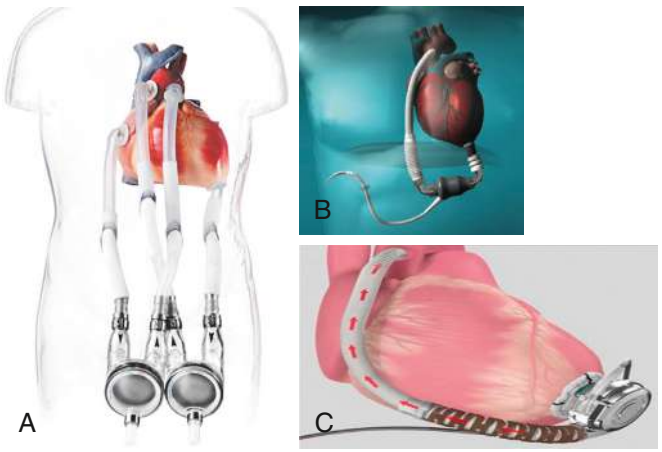


Fig. 491.5 Commonly used ventricular assist devices in children. **A,** Paracorporeal pneumatic pulsatile Berlin Heart EXCOR. **B** and **C,** Continuous flow devices: **(B)** HeartMate3; **(C)** HeartWare HVAD. *(A courtesy Berlin Heart, LLC; B from St. Jude Medical; C courtesy Medtronic, Inc.)*

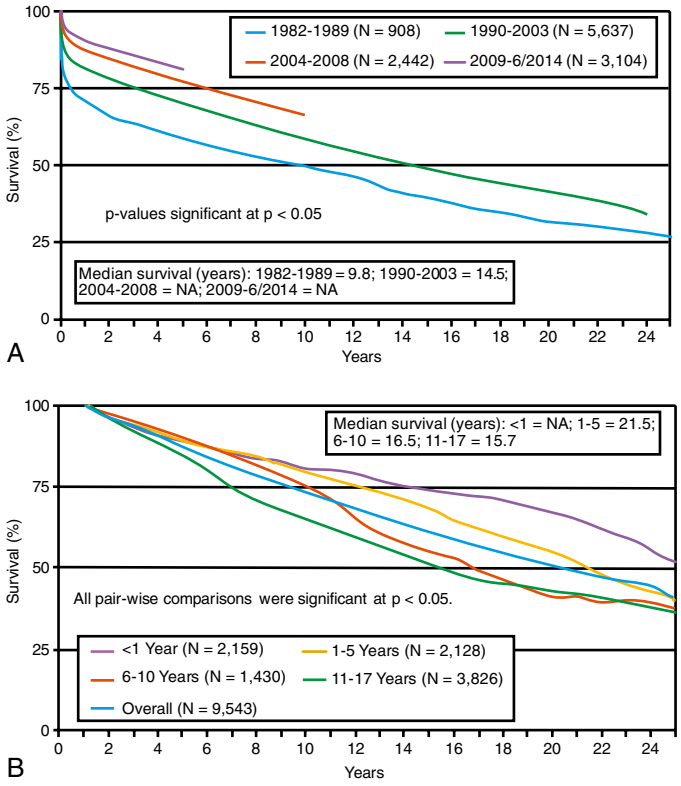


Fig. 492.1 A, Survival after pediatric heart transplantation comparing current and past eras. **B,** Long-term survival among patients that lived to 1-yr post-transplant. NA, Not applicable. *(From Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35[10]:1185–1195, Figs. 6 and 7.)*

Chapter 492

Pediatric Heart and Heart-Lung Transplantation

492.1 Pediatric Heart Transplantation

Danielle S. Burstein and Joseph W. Rossano

Pediatric heart transplantation is considered the standard therapy that offers long-term survival for end-stage heart disease in children. In adults, ventricular assist devices (VADs) are usually employed as a long-term therapy for patients not eligible for heart transplantation, but in children the vast majority of VADs are used as a *bridge* to transplantation as opposed to an alternative to transplantation. According to the International Society for Heart and Lung Transplantation, as of January 2019, over 14,000 heart transplants had been performed on children in the world, with about 400 transplants annually—a quarter of these in children <1 year of age. Survival rates have improved significantly over time, with most of the improvement occurring in the early period after transplant. This period continues to the associated with the greatest risk of death, and many patients who survive the first year after transplant are alive 20 years later (Fig. 492.1). Indeed, a growing number of patients receiving a heart transplant in childhood are approaching their 15-, 20-, and 30-year posttransplant anniversaries. Current (2011-2023) 1-year survival is ~90% and 5-year survival ~80%.

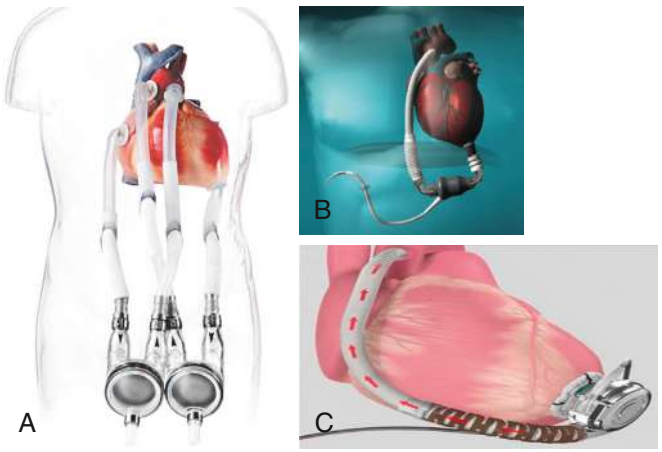
INDICATIONS

Heart transplantation is performed (1) in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, (2) in patients with previously repaired or palliated congenital heart disease (CHD) who have developed ventricular dysfunction or other nonoperable late-term complications, and (3) less frequently in patients with complex CHD—pulmonary atresia with intact septum and coronary arterial stenoses and some forms of hypoplastic left heart syndrome (HLHS)—for whom standard surgical procedures are extremely high risk. Additionally, **retransplantation** accounts for approximately 5% of transplants annually.

Cardiomyopathies account for >50% of heart transplants in pediatric patients older than 1 year, with the percentage of patients with previously repaired complex CHD at approximately 30%. In infants younger than 1 year, CHD previously represented >80% of transplants; this has decreased to 60% as standard surgical results for complex CHD (e.g., HLHS) have improved.

RECIPIENT AND DONOR SELECTION

Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of **pulmonary vascular disease**, which, if severe enough, would also preclude heart transplantation. Therefore pulmonary vascular resistance (PVR) is measured at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated PVR above 6 index Wood units are at higher risk for heart transplantation and may be considered candidates for heart-lung transplantation (see Chapter 492.2). However, with advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevation in PVR can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent must be obtained, indicating that the family (and, if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring.



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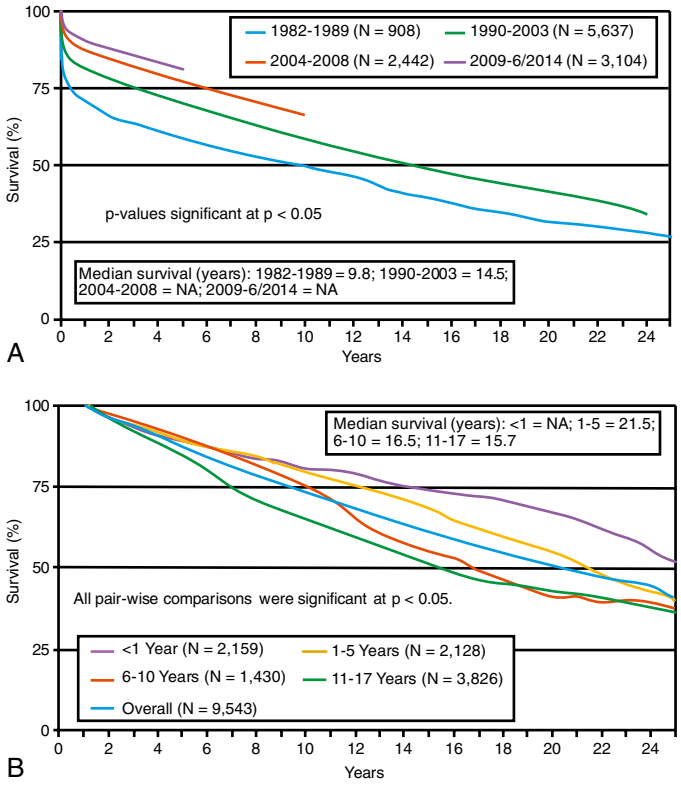

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Donor shortage is a serious problem for both adults and children. At the national registry of transplant recipients in the United States, the **United Network for Organ Sharing (UNOS)**, allografts are matched by ABO blood group and body weight. However, ABO matching may not be required for young infants less than 2 years of age because of the immaturity of the immune system. Patients, especially with a history of CHD, who have undergone prior operations may have antibodies against human leukocyte antigens (HLAs). Patients with elevated anti-HLA antibodies are at risk for a positive cross match and early graft dysfunction. These antibodies can also contribute to late graft dysfunction through antibody-mediated rejection and development of cardiac allograft vasculopathy. For patients with these elevated antibodies, there are strategies to avoid a positive cross match through a prospective cross match or a virtual cross match, although this may prolong the waiting list time. There are also desensitization therapies that may reduce circulating HLA antibody production, although they do not affect historical antibodies, and current data remain unclear how effective desensitization therapy is for reducing posttransplant rejection risk. Contraindications to organ donation include prolonged cardiac arrest with persistent moderate to severe cardiac dysfunction, ongoing systemic illness or infection, and preexisting severe cardiac disease. Physicians caring for a patient who may be a potential donor should always contact the organ donor coordinator at their institution, who can best judge the appropriateness of organ donation and has experience in interacting with potential donor families. A history of resuscitation alone or reparable CHD is not an automatic exclusion for donation.

The decision of when to place a patient on the transplant waiting list is based on many factors, including degree of ventricular function, markedly decreased exercise tolerance as determined by cardiopulmonary exercise testing (see Chapter 472.5), poor response to medical heart failure therapy, multiple hospitalizations for heart failure, arrhythmia, progressive deterioration in renal or hepatic function, early stages of pulmonary vascular disease, and poor nutritional status. Patients with severe ventricular dysfunction are often started on a regimen of anticoagulation to reduce the risk of mural thrombosis and thromboembolism. Patients with progressive heart failure resulting in decreases in end-organ (renal or hepatic) function unresponsive to standard pharmacologic treatment may be candidates for a VAD. The use of these devices has increased dramatically over the past decade, and currently over half of patients with dilated cardiomyopathy are on VAD support before transplant. VADs can improve hemodynamics and end-organ function, allow for rehabilitation, and allow some patients to be discharged home on VAD support (see Chapter 491).

PERIOPERATIVE MANAGEMENT

Heart transplantation in children can be performed either with a *biatrial* or *bicaval* anastomosis. In the *biatrial* anastomosis, both donor and recipient hearts are excised so that the posterior portions of the atria containing the venae cavae and pulmonary veins are left intact. The aorta and pulmonary artery are divided above the level of the semilunar valves. The anterior portions of the donor's atria are then connected to the remaining posterior portions of the recipient's atria, thereby avoiding the need for delicate suturing of the venae cavae or pulmonary veins. Previously, the donor and recipient great vessels were connected via end-to-end anastomoses. This has been supplanted in many centers by the *bicaval* anastomosis, with the donor right atrium (and sinus node) left intact and the suture lines at the superior and inferior vena cavae; the left atrial connection is still performed as in the *biatrial* anastomosis.

In the immediate postoperative period, **immunosuppression** is achieved with induction therapy that includes an antilymphocyte therapy for the first 5-7 days; common agents include antithymocyte globulin (ATG) and the humanized anti–interleukin-2 receptor antibodies (basiliximab). Steroids are also commonly used within the first 5-7 days and then are often weaned off or discontinued. Antiproliferative agents (mycophenolate mofetil [MMF]) are also started immediately after transplant and are transitioned to an oral compound once enteral medications are tolerated. The most common combinations of chronic immunosuppression are a *calcineurin inhibitor* (CNI; tacrolimus or cyclosporine) plus an *antiproliferative agent* (MMF or azathioprine). Mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) may be added to decrease the dose of CNI if renal insufficiency occurs. Many centers do not use steroids as part of maintenance immunosuppression but do use them as bolus treatment for acute rejection episodes. Immunosuppression levels are usually reduced after the first year posttransplant if there are no significant concerns for rejection. An ongoing U.S. multicenter pediatric trial called the TEAMMATE trial is comparing conventional immunosuppression therapy (tacrolimus and mycophenolate) with low-dose tacrolimus with everolimus and mycophenolate to determine which combination of immunosuppression is better at improving long-term pediatric post–heart transplant outcomes.

Many pediatric heart transplant recipients can be extubated from endotracheal intubation and mechanical ventilation support within the first 48 hours after transplantation and are out of bed in several days. In patients with preexisting high-risk factors, postoperative recovery may be considerably prolonged. For those with preoperative pulmonary hypertension, the use of nitric oxide in the postoperative period can allow the donor right ventricle to hypertrophy in response to elevated pulmonary artery pressures. Occasionally, these patients will require extracorporeal membrane oxygenation (ECMO) for primary graft dysfunction.

DIAGNOSIS AND MANAGEMENT OF ACUTE GRAFT REJECTION

Posttransplantation management consists of adjusting medications to maintain a balance between the risk of rejection and the side effects of over-immunosuppression. **Acute graft rejection** is a leading cause of death in pediatric heart transplant recipients. The incidence of acute rejection is greatest in the first 3 months after transplantation and decreases considerably thereafter. Many pediatric patients experience at least one episode of acute rejection in the first 2 years after transplantation, although modern immunosuppressive regimens have decreased the frequency of severe rejection episodes. Because the symptoms of rejection can mimic many routine pediatric illnesses (e.g., pneumonia, gastroenteritis), the transplant center should be notified whenever a heart transplant recipient is seen in the pediatrician's office or emergency department for acute illnesses.

Clinical manifestations of acute rejection may include fatigue, fluid retention, fever, diaphoresis, abdominal symptoms, and a gallop rhythm. The electrocardiogram (ECG) may show reduced voltage, atrial or ventricular arrhythmias, or heart block but is usually nondiagnostic. X-ray examination may show an enlarged heart, effusions, or pulmonary edema but typically only in the more advanced stages of rejection. Natriuretic peptide levels are usually increased during episodes of acute rejection. Most rejection episodes occur without any detectable clinical symptoms. On echocardiography, indices of systolic left ventricular function may be decreased; however, these usually do not deteriorate until rejection is at least moderately severe. Techniques to evaluate wall thickening and left ventricular diastolic function have not fulfilled their promise as predictors of early rejection. Most transplant centers do not rely on echocardiography alone for rejection surveillance.

Myocardial biopsy is the most reliable method of monitoring patients for rejection. Biopsy specimens are taken from the right ventricular side of the interventricular septum and can be harvested relatively safely, even in small infants. In infants, surveillance biopsies are usually performed less often and may be as infrequent as once or twice per year. Children may have clinically unsuspected rejection episodes even 5-10 years after transplantation; most pediatric transplant centers continue routine surveillance biopsies, although at less frequent intervals. Cardiac MRI evaluation has been an effective noninvasive method to perform rejection surveillance and to diagnose actual rejection.

Gene expression profiling of peripheral blood mononuclear cells has been validated in adults as a highly sensitive, moderately selective method of rejection surveillance. These results have not been confirmed in children. Other promising current techniques include the profiling of donor cell–free DNA released in the serum of patients during episodes of graft injury. Progress has also been made in genetic profiling as a means to determine which patients are most at risk for rejection. Children who have single nucleotide polymorphisms (SNPs) leading to greater activity of inflammatory cytokines or decreased activity of regulatory cytokines are at increased risk of rejection.

Cardiac rejection can be classified as cellular, antibody-mediated, or mixed. Criteria for grading cellular rejection are based on a system developed by the **International Society for Heart and Lung Transplantation (ISHLT)** that considers the degree of cellular infiltration and whether myocyte necrosis is present. ISHLT rejection grade 1R is usually mild enough that it is often not treated with bolus steroids, and many of these episodes resolve spontaneously. For patients with ISHLT grade 2R rejection, treatment is instituted with either intravenous (IV) methylprednisolone or a "bump and taper" of oral prednisone. Asymptomatic patients further out from transplant with normal echocardiograms may be treated as outpatients. Patients with grade 3R, or anyone with hemodynamic instability, are admitted to the hospital for IV corticosteroid and potentially more aggressive antirejection therapy. For rejection episodes resistant to steroid therapy, additional therapeutic regimens include antilymphocyte preparation (antithymocyte globulin), methotrexate, or total lymphoid irradiation. Refractory rejection is often considered a contraindication for retransplantation because of the relatively poor outcomes compared with other indications for retransplantation.

Criteria for grading antibody-mediated rejection are based on a system developed by the ISHLT that considers histologic and immunopathologic findings. In contrast to cellular rejection, antibody-mediated rejection is mediated by circulating donor-specific antibodies (DSAs) and can be detected by immunostaining of the biopsy specimen for the complement component C4d, for macrophages expressing CD68, and for evidence of histologic damage. Antibody-mediated rejection is less responsive to standard therapies for acute cellular rejection (e.g., bolus corticosteroids) and has been treated with plasmapheresis, intravenous immunoglobulin (IVIG), the anti–CD20 monoclonal antibody rituximab, and the proteasome inhibitor bortezomib, all with mixed results. The long-term outcome of patients with persistent DSAs or antibody-mediated rejection is poor, with many having early graft failure and premature development of graft vasculopathy.

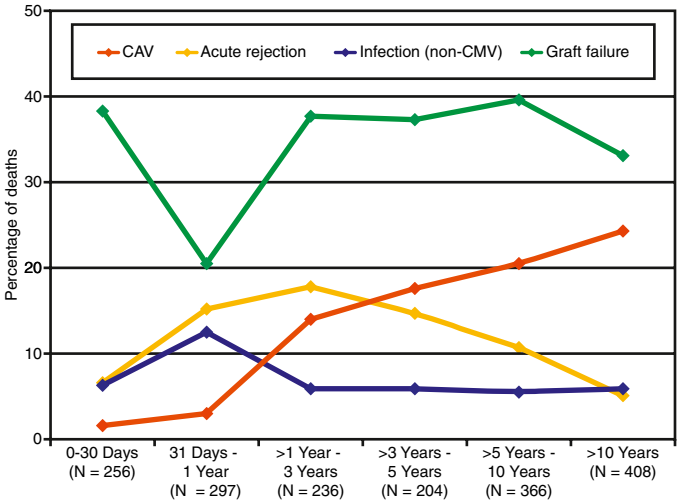

Fig. 492.2 Major causes of death after pediatric heart transplantation by time since transplant. CAV, Cardiac allograft vasculopathy; CMV, cytomegalovirus. *(From Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35[10]:1185–1195, Fig. 10.)*

COMPLICATIONS OF IMMUNOSUPPRESSION

Infection

Infection is also a leading cause of death in pediatric transplant patients (Fig. 492.2). The incidence of infection is greatest in the first 3 months after transplantation, when immunosuppressive doses are highest. **Viral** infections are most common and account for as many as 25% of infectious episodes. **Cytomegalovirus (CMV)** infection was once a leading cause of morbidity and mortality and may occur as a primary infection in patients without previous exposure to the virus or as a reactivation. Severe CMV infection can be disseminated or associated with pneumonitis or gastroenteritis and may provoke an episode of acute graft rejection or graft coronary disease. Most centers use IV ganciclovir or CMV immune globulin (Cytogam), or both, as prophylaxis in any patient receiving a heart from a donor who is positive for CMV or in any recipient who has serologic evidence of previous CMV disease. Oral preparations of ganciclovir with improved absorption profiles are available for chronic therapy, usually for 3-6 months after transplant, and have largely replaced IV preparations for prophylaxis. These regimens have significantly reduced the burden of CMV disease in heart transplant patients. Polymerase chain reaction (PCR) enhances the ability to diagnose CMV infection and monitor the efficacy of therapy serially.

Most normal childhood viral illnesses are well tolerated and do not usually require special treatment. Otitis media and routine upper respiratory tract infections can be treated in the outpatient setting, although fever or symptoms that last beyond the usual course require further investigation. **Gastroenteritis**, especially with vomiting, can result in greatly reduced absorption of immunosuppressive medications and provoke a rejection episode. In this setting, drug levels should be closely monitored and use of IV medications considered. Gastroenteritis can also be a sign of rejection, so a high index of suspicion must always be maintained. Varicella is another childhood illness of concern for immunosuppressed patients. If a heart transplant recipient acquires clinical varicella infection, treatment with IV acyclovir usually attenuates the illness.

Bacterial infections occur next in frequency after viral, with the lung the most common site of infection, followed by blood, urinary tract, and less often, the sternotomy site. Other sources of posttransplantation infection include fungi and protozoa. Many centers use trimethoprim-sulfamethoxazole for prophylaxis during the first several months after transplant to prevent *Pneumocystis jiroveci* infection.

Growth Stunting

Patients requiring chronic corticosteroid therapy usually have decreased linear growth. Thus many pediatric transplant programs aim for steroid-free immunosuppression within the first year after transplant. In patients who experience rejection when steroids are withdrawn, alternate-day corticosteroid regimens may result in improved linear growth. **Total lymphoid irradiation** has also shown promise as a steroid-sparing protocol. Despite these concerns, the majority of long-term survivors of pediatric heart transplantation have normal growth.

Hypertension

Hypertension is common in patients treated with CNIs, caused by a combination of plasma volume expansion and defective renal sodium excretion. Corticosteroids usually potentiate calcineurin-induced hypertension.

Renal Function

Chronic administration of cyclosporine or tacrolimus can lead to a tubulointerstitial nephropathy in adults, but severe renal dysfunction is less common in children. Most pediatric patients gradually have an increase in serum creatinine in the first year after transplantation; if renal dysfunction occurs, it usually responds to a decrease in CNI dosage. The addition of sirolimus, an mTOR inhibitor, allows a reduction in CNI dose in patients with renal dysfunction, although it is unclear whether this strategy leads to long-term improved renal function. Infection with BK virus, a growing problem in renal transplant patients, has been described as a source of renal dysfunction in heart transplant patients. Fortunately, pediatric heart transplant patients infrequently require dialysis or renal transplantation.

Neurologic Complications

Neurologic side effects of cyclosporine and tacrolimus include tremor, myalgias, paresthesias, and, rarely, seizures. These complications can be treated with reduced doses of medication and occasionally with oral magnesium supplementation. A rare form of encephalopathy known as **posterior reversible encephalopathy syndrome** (PRES) can occur in patients taking CNIs (cyclosporine or tacrolimus). PRES presents with hypertension, headaches, and seizures, requires MRI for diagnosis, and is usually managed by changing CNI or, in rare cases, eliminating CNIs totally in favor of other immunosuppressive agents (e.g., sirolimus, MMF).

Tumors

One of the serious complications limiting long-term survival in pediatric heart transplant patients is the risk of neoplastic disease. The most common is **posttransplant lymphoproliferative disease** (PTLD), a condition associated with Epstein-Barr virus (EBV) infection. Patients who are EBV seronegative at transplant (usually infants and young children) are at increased risk of developing PTLD if they subsequently seroconvert, acquiring the virus either from the donor organ or from primary infection. Unlike true cancer, many cases of PTLD respond to a reduction in immunosuppression. A monoclonal antibody directed against the CD20 antigen on activated lymphocytes (rituximab), in conjunction with steroids and cyclophosphamide therapy, has been effective against some forms of PTLD. However, PTLD can behave more aggressively, and many patients eventually require chemotherapy. An increased risk of skin cancer requires that children use appropriate precautions when exposed to sunlight.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a disease of the coronary arteries that occurs in approximately 20% of children 5 years after transplant. The cause is still unclear, although it is thought to be a form of immunologically mediated vessel injury. Multiple factors, including rejection episodes, infections, hypercholesterolemia, and hyperglycemia, are thought to increase the risk of CAV. Unlike native coronary atherosclerosis, CAV is a diffuse process with a high degree of distal vessel involvement. Because the transplanted heart has been denervated, patients may not experience symptoms such as angina pectoris during ischemic episodes, and the initial manifestation may be cardiovascular collapse or sudden death. Most centers perform coronary angiography annually to screen for coronary abnormalities; some also perform coronary intravascular ultrasound in larger children and adolescents. Standard coronary artery bypass procedures are usually not helpful because of the diffuse nature of the process, although transcatheter stenting can sometimes be effective for isolated lesions. For patients with severe CAV, repeat heart transplantation has been the only effective treatment. Thus prevention has been the focus of most current research. The cell-cycle inhibitors sirolimus and everolimus have been shown to decrease coronary arterial intimal thickening in adult transplant patients. Cholesterol-lowering HMG-CoA (3-hydroxy-3-methyl-coenzyme A) reductase inhibitors (e.g., pravastatin, atorvastatin) have been associated with a lower risk of CAV.

Other Complications

Corticosteroids usually result in cushingoid facies, steroid acne, and striae. Cyclosporine can cause a subtle change in facial features, such as hypertrichosis and gingival hyperplasia. These cosmetic features can be particularly disturbing to adolescents and may be the motivation for noncompliance, one of the leading risks for late morbidity and mortality. Most of these cosmetic complications are dose related and improve as immunosuppressive medications are weaned. Tacrolimus does not have the cosmetic side effects of cyclosporine. Osteoporosis and aseptic necrosis are additional reasons for reducing the steroid dosage as soon as possible. Diabetes and pancreatitis are rare but serious complications.

Rehabilitation

Despite the potential risks of immunosuppression, the prospect for rehabilitation in pediatric heart transplant recipients is excellent; most have no functional limitations in their daily lives. They can attend daycare or school and participate in competitive sports and other age-appropriate activities. Standardized measurements of ventricular function are close to normal. Because the transplanted heart is denervated, the increase in heart rate and cardiac output during exercise is slower in transplant recipients, and maximal heart rate and cardiac output responses are mildly attenuated. These subtle abnormalities are rarely noticeable by the patient.

Growth of the transplanted heart is excellent, although a mild degree of ventricular hypertrophy is often seen, even years after transplantation. The sites of atrial and great vessel anastomoses usually grow without the development of obstruction. In neonates who undergo transplantation for HLHS, however, juxtaductal aortic coarctation may recur.

A serious problem with noncompliance may occur once patients reach adolescence, and life-threatening rejection may result. Early intervention by social workers, counselors, and psychologists may be able to reduce this risk.

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492.2 Heart-Lung and Lung Transplantation

Samuel B. Goldfarb, Danielle S. Burstein, and Joseph W. Rossano

More than 700 heart-lung and 2,500 lung (single or double) pediatric transplants have been performed and reported to ISHLT, with >100 procedures performed annually. The majority of these are lung transplantation, with only three heart-lung transplants reported in 2017. Only 16 heart-lung transplants have been performed in the United States in the past 5 years compared to over 140 lung transplants during this same time frame. Primary indications for lung transplantation include cystic fibrosis, pulmonary hypertension, interstitial lung disease, surfactant deficiencies, and retransplant. Indications for heart-lung transplant include complex CHD along with either pulmonary parenchymal or vascular disease. Patients with normal hearts are candidates for lung transplantation even in the setting of right ventricular dysfunction. This had led to the marked decline in heart-lung transplant procedures in the current era. In some patients with CHD, double-lung transplantation can be performed in combination with repair of intracardiac defects. Patients with cystic fibrosis are *not* candidates for single-lung grafts

because of the risk of infection from the diseased contralateral lung. Patients are selected according to many of the same criteria as for heart transplant recipients (see Chapter 492.1).

Posttransplant immunosuppression is usually achieved with a triple-drug regimen, combining a CNI (cyclosporine or tacrolimus) with an antiproliferative agent (MMF or azathioprine) and prednisone. Most patients receive induction therapy with an antithymocyte or anti–T-cell preparation. Unlike patients with isolated heart transplants, patients with lung or heart-lung transplants cannot be weaned totally off steroids. Prophylaxis against *P. jiroveci* infection is achieved with trimethoprim-sulfamethoxazole or aerosolized pentamidine. Ganciclovir and CMV immune globulin prophylaxis are used as in heart transplant recipients (see Chapter 492.1). Antifungal medications are used in the perioperative and posttransplant periods in patients who have pretransplant colonization.

Pulmonary rejection is common in lung or heart-lung transplant recipients, whereas heart rejection is encountered much less often than in patients with isolated heart transplants. Acute cellular rejection (ACR) occurs in approximately 10–30% of patients in the first year after transplant depending on the recipient's age. Younger recipients have a lower incidence of ACR. Antibody-mediated rejection (AMR) and chronic lung allograph dysfunction (CLAD) are other forms of rejection. Symptoms of lung rejection may include fever and fatigue, although many episodes are minimally symptomatic. Signs of rejection could include changes in lung function testing and radiographic findings. Surveillance for acute rejection is performed by monitoring pulmonary function (forced vital capacity; forced expiratory volume in 1 second [FEV_1]; forced expiratory flow, midexpiratory phase [$FEF_{25–75\%}$]), systemic arterial oxygen tension, chest radiographs, chest CT, transbronchial biopsy, and open lung biopsy. The gold standard for ACR is tissue diagnosis, generally performed with transbronchial biopsies. AMR is diagnosed based on findings of donor-specific antibodies and tissue biopsy often associated with graft dysfunction. CLAD is a form of chronic rejection. It can present as an obstructive lung disease in the form of obliterative bronchiolitis. CLAD can also present with significant pulmonary fibrosis in the form of restrictive allograft dysfunction (RAD). In heart-lung transplant recipients, hearts are assessed for rejection similar to the approach described in Chapter 492.1.

Actuarial survival rates after lung or heart-lung transplantation in children are currently 75–80% at 1 year and 50% at 5 years after transplant; improved patient selection and postoperative management are continually improving these survival statistics from prior eras. In the analysis of survival at 5 years conditional on survival at 12 months, rates significantly improve for both lung and heart-lung regardless of underlying condition. One year conditional survival rates at 5 years for both are roughly 70%. Some groups, such as patients with CHD in the absence of Eisenmenger syndrome, have particularly poor outcomes with transplant. Graft failure and infection are the leading cause of early death, whereas a form of chronic rejection in the form of CLAD or RAD accounts for almost 50% of cases of late mortality. Other causes of early morbidity and mortality include technical complications, multiorgan failure, primary graft dysfunction, and cardiovascular causes. Additional late complications include the development of late graft failure, malignancies, infection, and other side effects of chronic immunosuppression.

Postoperative indices of cardiopulmonary function and exercise capacity show significant improvement. Problems of donor availability are even more severe with lung transplantation than with isolated heart transplantation. However, significant advances in ex vivo lung perfusion have great potential to expand the number of organs available for transplantation.

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Section 8

Diseases of the Peripheral Vascular System

Chapter 493

Diseases of the Blood Vessels (Aneurysms and Fistulas)

493.1 Aneurysms

Daniel Bernstein

See also Chapter 208.

Aneurysms of the coronaries and occasionally the systemic arteries may complicate Kawasaki disease and are the leading cause of morbidity in this disease (Figs. 493.1 and 493.2). Persistent moderate to large aneurysms carry several risks: embolism and thromboembolism (a clot developing in the aneurysm because of stagnant blood flow and obstructing flow and/or breaking off and traveling more distally down the coronary, resulting in myocardial ischemia/infarction) and stenosis (the distal end of the aneurysm tends to become narrowed over time, limiting downstream coronary blood flow). Management includes anticoagulation to prevent thrombosis and β blockers to reduce myocardial oxygen requirements (see Chapter 210).

COVID-19–associated multisystem inflammatory syndrome in children (MIS-C) typically occurs a few weeks after active SARS-CoV-2 infection and can cause coronary artery dilation and aneurysms, in addition to other significant cardiac manifestations (ventricular dysfunction, arrhythmias, and conduction abnormalities; see Chapters 311 and 449.1).

Other than in Kawasaki disease and MIS-C, aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus, Ehlers-Danlos syndrome type IV (vascular ecchymotic form), hyper-IgE syndrome, Marfan syndrome, and the four forms of Loeys-Dietz syndrome (see Chapter 641). Aneurysms may be seen in the arterial tortuosity syndrome and the multisystem smooth muscle dysfunction syndrome (MSMDS) (see Chapter 493.4). MSMDS is characterized by congenital mydriasis, patent ductus arteriosus, aortic and other arterial aneurysms, as well as moyamoya-like cerebrovascular disease and pulmonary hypertension. The affected gene is *ACTA2*. Aneurysms may also occur secondary to an infected embolus; infection contiguous to a blood vessel; trauma; congenital abnormalities of vessel structure, especially the medial wall; and arteritis, including polyarteritis nodosa, Behçet syndrome, and Takayasu arteritis (see Chapter 210.2).

493.2 Arteriovenous Fistulas

Daniel Bernstein

Arteriovenous fistulas may be limited and small or may be large and extensive, producing systemic complications (see Chapters 554 and 691). The most common sites in infants and children are within the

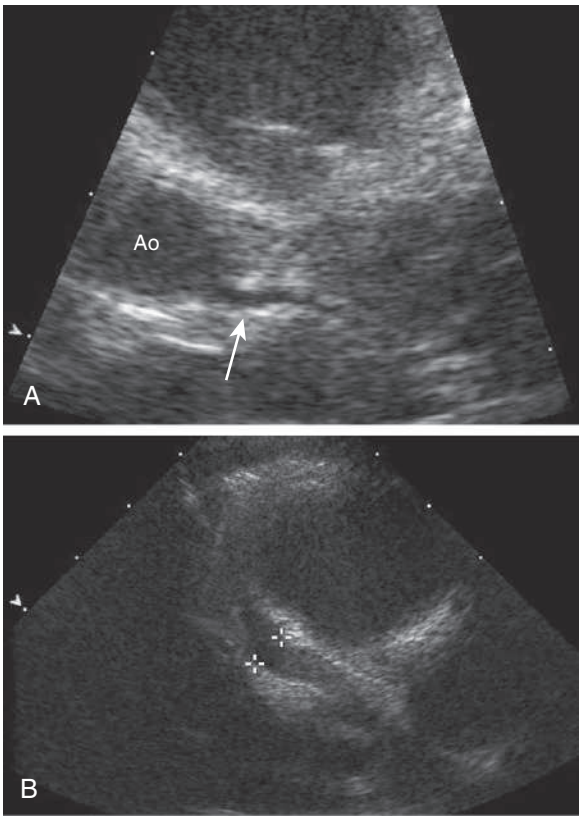

Fig. 493.1 Two-dimensional echocardiograms comparing a normal left main coronary artery (*arrow* in A) with a giant coronary artery aneurysm (outlined by *cross marks* in B) in a patient with Kawasaki disease. Ao, Aorta.

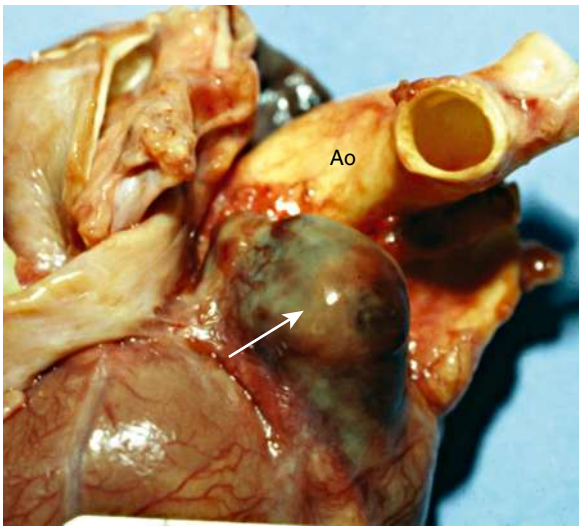

Fig. 493.2 Pathologic specimen showing giant aneurysm of left main coronary artery *(arrow)*. Ao, Ascending aorta.

cranium, in the liver, in the lung, in the extremities, and in vessels in or near the thoracic wall. These fistulas, although usually **congenital**, may follow trauma or may be a manifestation of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Femoral arteriovenous fistulas are a rare complication of percutaneous femoral catheterization.

CLINICAL MANIFESTATIONS

Clinical symptoms occur only in association with large arteriovenous communications when arterial blood flows into a low-pressure venous system without the resistance of the capillary bed; local venous pressure is increased, and arterial flow distal to the fistula is decreased. Systemic arterial resistance falls because of the runoff of blood through the fistula. Compensatory mechanisms include tachycardia and increased stroke volume so that cardiac output rises. Total blood volume is also increased. In large fistulas, left ventricular dilation, a widened pulse pressure, and high-output heart failure can occur. CT, MRI, or injection of contrast material into an artery proximal to the fistula confirms the diagnosis.

Large intracranial arteriovenous fistulas most often occur in newborn infants in association with a **vein of Galen malformation**. The large intracranial left-to-right shunt results in heart failure secondary to the demand for high cardiac output. Patients with smaller communications may not have cardiovascular manifestations but may later be disposed to hydrocephalus (see Chapter 631.9) or seizures. The diagnosis can often be made by auscultation of a continuous murmur over the cranium. Older children with more diffuse intracranial arteriovenous malformations may be recognized on the basis of intracranial calcification and high cardiac output without cardiac failure.

Coronary arteriovenous fistulas can develop between a coronary artery and any of the cardiac chambers **(coronary cameral fistula)** or great vessels. These fistulas can result in steal of blood away from the heart muscle downstream of the fistula resulting in ischemia and, in rare cases, can even cause obstruction of ventricular inflow caused by physical interference with atrioventricular valve function.

Hepatic arteriovenous fistulas may be generalized or localized in the liver and may be hemangioendotheliomas or cavernous hemangiomas. The fistula may be located between the hepatic artery and the ductus venosus or portal vein. Congenital hemorrhagic telangiectasia may also be present. Large arteriovenous fistulas are associated with increased cardiac output and heart failure. Hepatomegaly is usual, and systolic or continuous murmurs may be audible over the liver.

Peripheral arteriovenous fistulas generally involve the extremities and can be associated with disfigurement, swelling of the extremity, and visible hemangiomas. Their presence can be complicated by breathing difficulties if located near the upper airways and causing obstruction. Because only a small minority results in large arterial runoff, cardiac failure is uncommon.

TREATMENT

Medical management of heart failure is initially helpful in neonates with these conditions; with time, the size of the shunt may diminish and symptoms spontaneously regress. Hemangiomas of the liver often eventually disappear completely. Large liver hemangiomas have been treated with corticosteroids, β blockers, ε-aminocaproic acid, interferon, local compression, embolization, or local irradiation; the beneficial effects of these management options are not firmly established because individual patients display marked variation in clinical course without treatment. **Transcatheter closure** is becoming the treatment of choice for many patients with a symptomatic arteriovenous fistula. Embolic agents that have been used include detachable balloons, steel (Gianturco) coils, plugs, and liquid tissue adhesives (cyanoacrylate). Often, multiple procedures are necessary before flow is significantly reduced. **Gamma knife radiosurgery** has been used successfully in patients with cerebral arteriovenous malformations. Surgical removal of a large fistula may be attempted in patients with severe cardiac failure and lack of improvement with medical treatment. Surgical treatment may be contraindicated or unsuccessful when the lesion is extensive and diffuse or is located in a position where adjoining tissue may be injured during the surgery or related procedures. β-Adrenergic blockers such as propranolol have dramatically changed the treatment for cutaneous hemangiomas, with excellent results.

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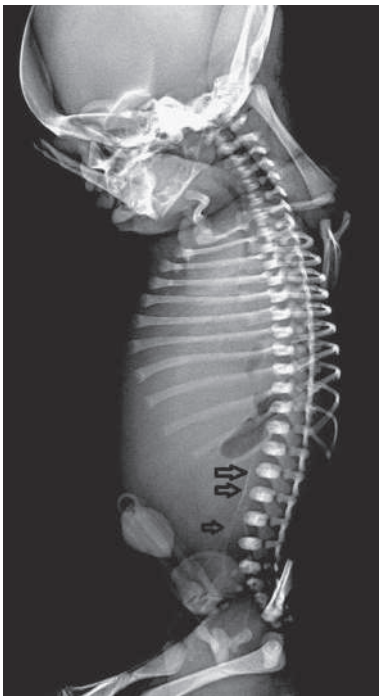

Fig. 493.3 Lateral radiograph of the neonate showing calcification of the descending aorta and its bifurcation *(arrows). (From Karthikeyan G. Generalized arterial calcification of infancy. J Pediatr. 2013;162:1074, Fig 3.)*

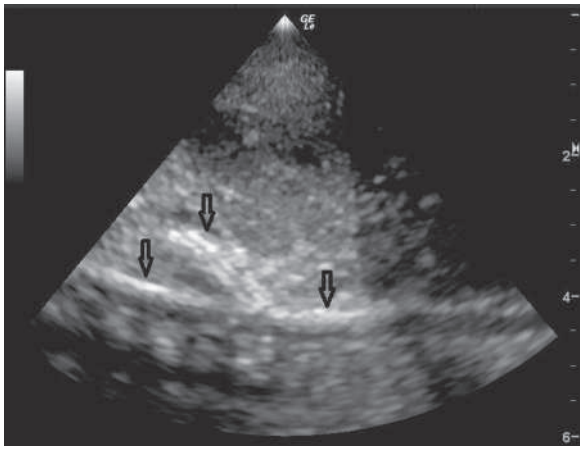

Fig. 493.4 Ultrasonography of abdominal aorta showing calcification of descending aorta and its branches *(arrows). (From Karthikeyan G. Generalized arterial calcification of infancy. J Pediatr. 2013;162:1074, Fig. 1.)*

493.3 Generalized Arterial Calcification of Infancy (Idiopathic Infantile Arterial Calcification)

Robert M. Kliegman

Generalized arterial calcification of infancy (GACI) is a rare and often lethal autosomal recessive disorder characterized by calcification of muscular arteries with fibrotic myointimal proliferation and subsequent vascular stenosis leading to tissue ischemia, poor function, or infarction. Diffuse arterial calcification may begin in utero, leading to hydrops fetalis; in the neonate, diffuse arterial calcification leads to respiratory distress and heart failure or myocardial infarction (coronary, pulmonary arteries), hypertension (renal arteries), and poor femoral pulses (aorta, femoral arteries).

Pathogenic variants in the ectonucleotide pyrophosphatase 1 gene (*ENPP1*) are noted in 75% of patients. Serum calcium, phosphate, and alkaline phosphatase levels are normal; the vascular calcification may be seen on plain x-ray films (Fig. 493.3), ultrasonography (Fig. 493.4), or CT scans (Fig. 493.5), which may reveal calcifications not visible on plain films.

A subset of patients with GACI have monoallelic or biallelic pathogenic variants in the adenosine triphosphate–binding cassette subfamily C number 6 gene (*ABCC6*), which is responsible for **pseudoxanthoma elasticum** (PXE). PXE, an autosomal recessive disorder, is classically associated with a later onset of ectopic mineralization of elastic fibers in the skin, eyes, joints, and arteries. In addition, some surviving infants with *ENPP1* variant develop PXE symptoms involving the skin and retina (angioid streaking).

Infants with GACI have been treated with bisphosphonates with variable success. In addition, some survivors with the *ENPP1* variant have developed hypophosphatemic-hyperphosphaturic rickets.

In the absence of stroke or encephalomalacia, most survivors are developmentally normal. In some survivors the vascular calcification resolves and is replaced by fibrosis. The differential diagnosis includes Singleton-Merten syndrome (aortic calcification, dental anomalies, osteopenia), hypervitaminosis D, hyperparathyroidism, congenital syphilis (aortitis), twin-twin transfusion syndrome (recipient), and idiopathic iliac artery calcification of infancy.

ARTERIAL CALCIFICATIONS CAUSED BY DEFICIENCY OF CD73

This rare autosomal recessive disorder, caused by pathogenic variants in the 5-exonucleotidase CD73 *(NT5E)*, results in joint and arterial (lower-extremity) calcification in adults. Patients present with intermittent claudication and joint pain. Onset is probably before adulthood, since patients may be undiagnosed with nonspecific findings during adolescence.

493.4 Arterial Tortuosity

Robert M. Kliegman

Arterial tortuosity may be seen in many different diseases and genes (Table 493.1). These disorders are usually recognized by their phenotype, and all may present during childhood. Tortuosity is best defined by magnetic resonance angiography (Fig. 493.6). When present, it often increases the risk for early cardiovascular morbidity for patients with Marfan or Loeys-Dietz syndrome.

Arterial tortuosity syndrome is another genetic arteriopathy caused by pathogenic variants in the *SCL2A10* gene. It has many features of other connective tissue diseases, including hyperextensible and soft velvety skin, high-arched palate, micrognathia, abdominal hernias, and joint hypermobility. The prognosis for patients with arterial tortuosity syndrome is quite variable, but the presence of vascular stenosis is associated with a poorer prognosis.

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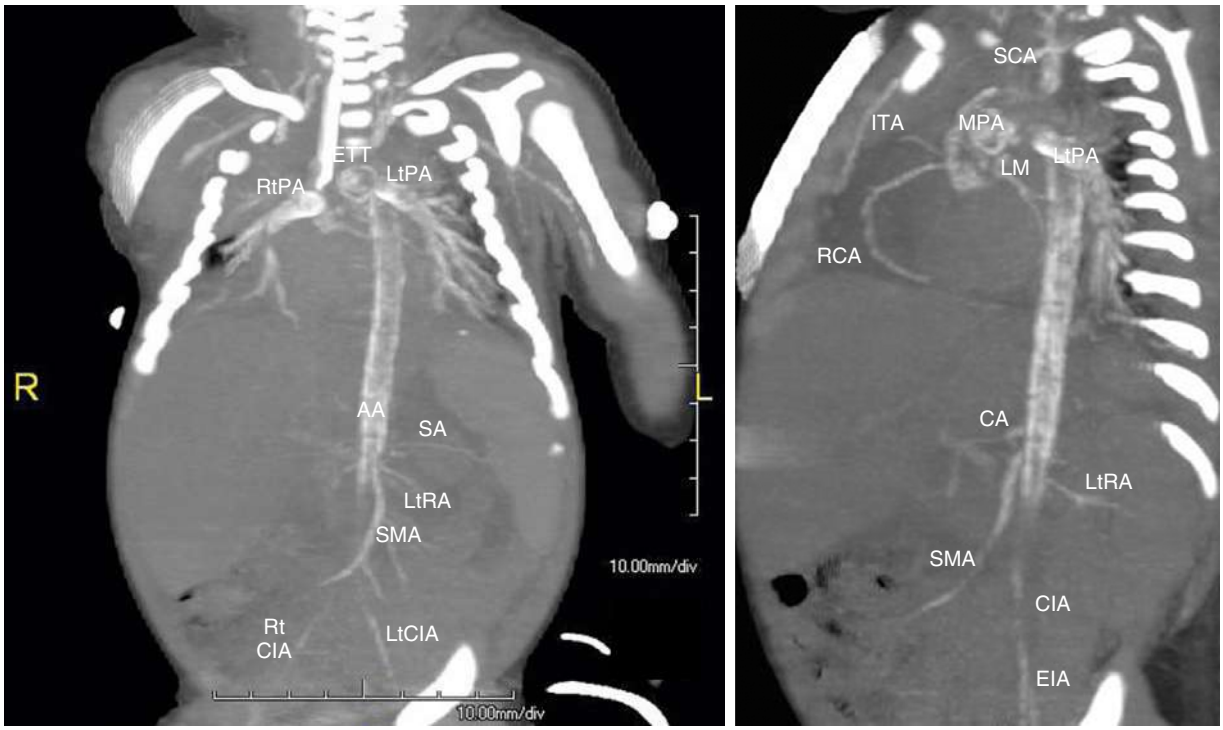

Fig. 493.5 Coronal maximum intensity projection (MIP) CT scans demonstrate an endotracheal tube (ETT) and extensive vascular calcifications. PA, Pulmonary artery; SA, splenic artery; RA, renal artery; CIA, common iliac artery; BA, brachial artery; CA, celiac axis; SMA, superior mesenteric artery; SCA, subclavian artery. *(From Bolster F, Ali Z, Southall P, et al. Generalized arterial calcification of infancy—findings at post-mortem computed tomography and autopsy. Forensic Sci Int. 2015;254:e7–e12, Fig 3.)*

Table 493.1 Genetic Disorders Associated with Aortic Disease and Arterial Tortuosity

GENE	DISORDER
TGFBR1	Loeys-Dietz syndrome, FTAAD
TGFBR2	Loeys-Dietz syndrome, FTAAD
FBN1	Marfan syndrome
SMAD3	Osteoarthritis-aneurysm syndrome, FTAAD
SLC2A10	Arterial tortuosity syndrome
TGFB2	FTAAD
PRKG1	FTAAD
FBLN4/EFEMP2	Cutis laxa
ATP7A	Occipital horn syndrome, Menkes syndrome
Monosomy X/mosaic monosomy X	Turner syndrome
FTAAD	Familial aortic aneurysm and dissection
ACTA2	Multisystem smooth muscle dysfunction syndrome

FTAAD, Familial thoracic aortic aneurysm and dissection.
Adapted from Morris SA. Arterial tortuosity in genetic arteriopathies. *Curr Opin Cardiol.* 2015;30:587–590, Table 1, p. 590.

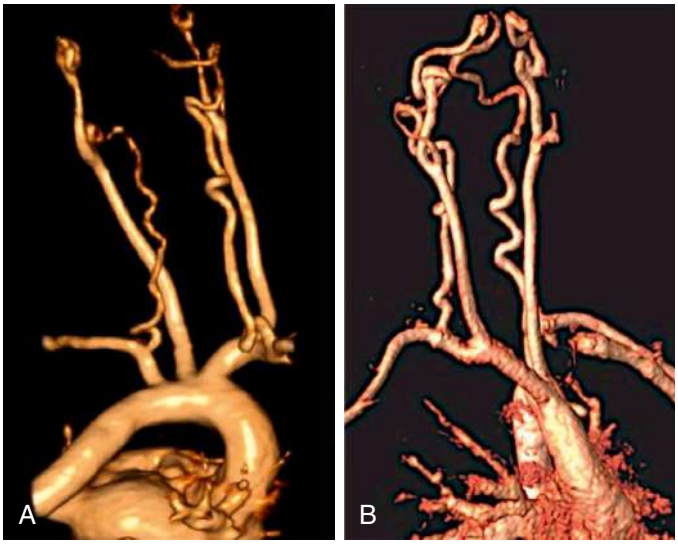

Fig. 493.6 Examples of vertebral artery tortuosity in Marfan syndrome with *FBN1* pathogenic variant (**A**) and Loeys-Dietz syndrome with a *TGFBR2* mutation (**B**). *(From Morris SA. Arterial tortuosity in genetic arteriopathies. Curr Opin Cardiol. 2015;30:587–593, Fig 1.)*

Chapter 494

Systemic Hypertension

Ian R. Macumber and Joseph T. Flynn

Hypertensive children, although frequently asymptomatic, already may manifest evidence of target organ damage. Up to 40% of hypertensive children have left ventricular hypertrophy, and hypertensive children have increased carotid intima-to-media thickness, a marker of early atherosclerosis. Primary (essential) hypertension occurring during childhood often continues into adulthood. Children with blood pressure (BP) >90th percentile exhibit a 2.4-fold greater risk of having hypertension as adults. Similarly, almost half of hypertensive adults had a BP >90th percentile as children. Adolescent hypertension is also an independent predictor of both end-stage kidney disease and left ventricular dysfunction in middle-age males.

PREVALENCE OF HYPERTENSION IN CHILDREN

In infants and young children, systemic hypertension is uncommon, with a prevalence of <1%, but, when present, often indicates an underlying disease process **(secondary hypertension)**. *Severe and symptomatic hypertension in children is usually caused by secondary hypertension.* In contrast, the prevalence of primary hypertension, mostly in older school-age children and adolescents, has increased in prevalence in parallel with the obesity epidemic. Estimates are variable, but data from the U.S. National Health and Nutrition Examination Survey (NHANES) show that approximately 9% of American youth have **elevated BP** and 3–4% have **hypertension**. A meta-analysis suggests a similar worldwide prevalence of hypertension in children. The normative data from the 2017 American Academy of Pediatrics (AAP) clinical practice guidelines have resulted in an overall trend of increased hypertension prevalence. The influence of obesity on elevated BP is evident in children as young as 2-5 years old. Approximately 20% of American youth have obesity, and up to 10% of these have hypertension.

DEFINITION OF HYPERTENSION

Normal BP in adults is <120/80 mm Hg. **Elevated** blood pressure is considered systolic BP of 120-129 *and* diastolic BP <80 mm Hg. **Stage 1** hypertension is systolic 130-139 *or* diastolic 80-89 mm Hg; **Stage 2** hypertension is systolic ≥140 *or* diastolic ≥90 mm Hg. This definition is based on potential outcomes because it relates degree of BP elevation with significant likelihood of subsequent cardiovascular events. Because hypertension-associated cardiovascular events (e.g., myocardial infarction, stroke) occur rarely in childhood, the definition of hypertension in children is statistical and based on the *distribution of BP in healthy children,* not outcomes. The AAP clinical practice guideline on childhood hypertension maintains the same statistical approach to defining and categorizing childhood BP as in previous guidelines from the **National High Blood Pressure Education Program (NHBPEP)**:

- **Normal BP:** BP <90th percentile for age, sex, and height or <120/<80 (systolic/diastolic) mm Hg for adolescents ≥13 years old
- **Elevated BP:** BP reading ≥90th percentile and <95th percentile for age, sex, and height or 120-129/<80 mm Hg for adolescents ≥13 years old
- **Hypertension:** BP >95th percentile for age, sex, and height or ≥130/80 mm Hg for adolescents ≥13 years old. Hypertensive-level BP is further staged as follows:
  - **Stage 1 hypertension:** BP >95th percentile for age, sex, and height up to the 95th percentile + 11 mm Hg or 130-139/80-89 mm Hg for adolescents ≥13 years of age
  - **Stage 2 hypertension:** BP ≥95th percentile + 12 mm Hg for age, sex, and height or >140/90 mm Hg for adolescents ≥13 years of age

The BP cut-points for adolescents ≥13 years old and use of the term *elevated BP* instead of prehypertension were chosen to align with revised BP cut-points and terminology found in the American Heart Association/American College of Cardiology (AHA/ACC) guideline for adult hypertension. The European Society of Hypertension (ESH) pediatric BP guideline also suggested that an absolute BP cutoff be used for adolescents age 16 and older, rather than using BP percentiles. For these older adolescents, the ESH guidelines define *high-normal* BP as 130-139/85-89 mm Hg and *hypertension* as ≥140/90 mm Hg.

The AAP guideline* also contains tables of normative BP values for children and adolescents based on a reanalysis of the NHBPEP database, removing all overweight and obese children. This revision results in BP values that are 2-3 mm Hg lower than the corresponding BP values in the 2004 NHBPEP Fourth Report, illustrating the impact of the childhood obesity epidemic on BP in young persons. The AAP guideline also contains a *simplified table* of BP values that may require further evaluation, which should be useful for screening (Table 494.1).

BLOOD PRESSURE MEASUREMENT IN CHILDREN

The AAP guideline recommends that children 3 years or older should have their BP measured during annual preventive visits, unless the child has risk factors such as obesity, chronic kidney disease (CKD), or diabetes, in whom it should be checked at every healthcare encounter. In contrast, the ESH pediatric guideline recommends checking BP at every healthcare encounter for all children >3 years old. Selected children <3 years old should also have their BP measured, including those with a history of prematurity, congenital heart disease, kidney disease, solid-organ transplant, cancer, treatment with drugs known to raise BP, other illnesses associated with hypertension (e.g., neurofibromatosis, tuberous sclerosis), or evidence of increased intracranial pressure. The preferred method is by auscultation using a sphygmomanometer (BP) with a cuff appropriate for the size of the child's arm.

Elevated readings should be confirmed on repeat visits before determining that a child is hypertensive. The BP should be measured with the child in the seated position after a period of quiet for at least 5 minutes, and it is recommended that the BP be checked 3 times, averaging the results. Careful attention to **cuff size** is necessary to avoid overdiagnosis, because a cuff that is too short or narrow artificially increases BP readings. An appropriate-sized cuff has an inflatable bladder whose length covers 80–100% of the upper arm circumference (measured midway between the acromion process and olecranon) and whose width is at least 40% of the arm circumference. A wide variety of cuff sizes should be available in any medical office where children are routinely seen.

Systolic blood pressure (SBP) is indicated by appearance of the *first* Korotkoff sound. Diastolic blood pressure (DBP) has been defined by consensus as the *fifth* Korotkoff sound, unless the Korotkoff sounds can be heard down to 0 mm Hg, in which case the *fourth* Korotkoff sound should be reported as the DBP. Palpation is useful for rapid assessment of SBP, although the palpated BP is generally about 10 mm Hg lower than that obtained by auscultation. Oscillometric techniques are used frequently in infants and young children, but they are susceptible to artifacts and are best for measuring mean arterial pressure (MAP). In addition, different devices use different proprietary algorithms to back-calculate SBP and DBP from the MAP, making comparison between devices difficult.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring **(ABPM)** is frequently used as a tool to assess pediatric hypertension. The patient wears a device that records BP every 20-30 minutes throughout a 24-hour period, during usual daily activities, including sleep. This monitoring allows calculation of the mean daytime BP, sleep BP, and mean

* https://publications.aap.org/pediatrics/article/140/3/e20171904/38358/Clinical-Practice-Guideline-for-Screening-and.

BP over 24 hours. The physician can also determine the proportion of BP measurements that are in the hypertensive range (BP load) and whether there is an appropriate decrease in BP during sleep (nocturnal dip), generally considered *normal* if there is a decrease in nocturnal BP of >10% from awake values. The cuff should be placed on the patient's nondominant arm. It is recommended that the patient keep a journal of sleep and awake times, medication timing, and other events that may be relevant to BP readings. Clinicians should only perform ABPM if they have had specific training in performing and interpreting the results.

ABPM readings are more strongly correlated with target-organ damage in children than casual/office BP readings and are more sensitive for a diagnosis of hypertension than either manual or automated office blood pressures. The 2017 AAP guideline strongly recommends that ABPM be performed on all patients with elevated office readings to confirm the diagnosis of hypertension. In addition, ABPM is necessary to diagnose **white coat hypertension** (elevated office BP but normal ambulatory BP) and **masked hypertension** (normal office BP but elevated ambulatory BP). It should be noted that white coat hypertension is not a benign condition, and children with white coat hypertension may be at increased risk of developing sustained hypertension in the future. In adults, white coat hypertension has been associated with higher all-cause and cardiovascular mortality compared to normotensive individuals. ABPM is also a useful tool for evaluating effectiveness of antihypertensive therapy. ABPM is recommended to assess BP patterns in high-risk patient populations, such as children with CKD, solid-organ transplant, diabetes mellitus, and severe obesity.

ABPM is an extremely useful tool for evaluating and managing hypertension in appropriate patient populations, but it does have limitations. Not every patient will tolerate APBM, including younger children (although there are reports of successful ABPM in toddlers 18 months old) and some children with developmental delay. Nonetheless, it is usually feasible to perform ABPM in children ≥6-7 years. The most accepted normative data come from the German Working Group on Pediatric Hypertension. However, there are concerns with this dataset: (1) it includes only Central European White children and thus might not be generalizable to other ethnicities; (2) there were relatively few shorter children included, which may limit its application to patients with chronic diseases such as CKD; and (3) there was very little variability in DBP values, which is not consistent with data from other BP measurement techniques showing that DBP varies with both age and height.

Table 494.1 Simplified Table of Screening Blood Pressure Values (mm Hg) Requiring Further Evaluation

	MALES		FEMALES	
AGE (YR)	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

From Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904, Table 6.

ETIOLOGY AND PATHOPHYSIOLOGY

Blood pressure is the product of cardiac output (CO) and peripheral vascular resistance (PVR). An increase in either CO or PVR results in an increase in BP; if either of these factors increases while the other decreases, BP may not increase. When hypertension is the result of another disease process, it is referred to as *secondary hypertension*. When no identifiable cause can be found, it is referred to as *primary hypertension*.

Secondary hypertension is most common in infants and younger children. It is most often caused by kidney abnormalities; additional etiologies include cardiovascular disease and endocrinopathies. Younger age, severely elevated BP, and symptomatic hypertension make a secondary cause of hypertension more likely. Many childhood diseases can be responsible for *chronic hypertension* (Table 494.2) or *acute/intermittent hypertension* (Table 494.3). The most likely cause varies with age. Hypertension in the premature infant is sometimes

Table 494.2 Conditions Associated with Chronic Hypertension in Children

RENAL
Recurrent pyelonephritis/renal scarring
Chronic glomerulonephritis
Prematurity
Congenital dysplastic kidney
Polycystic kidney disease
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Ask-Upmark kidney)
Obstructive kidney disease
Renal tumors
Renal trauma
Systemic lupus erythematosus (other connective tissue diseases)
VASCULAR
Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)
Renal vein thrombosis
Vasculitis (ANCA associated, polyarteritis nodosa, Takayasu arteritis)
Arteriovenous shunt
Williams-Beuren syndrome
Moyamoya disease
ENDOCRINE
Hyperthyroidism
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)
Cushing syndrome
Primary hyperaldosteronism
Apparent mineralocorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypoaldosteronism type 2 (Gordon syndrome)
Pheochromocytoma
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
Liddle syndrome
Geller syndrome
CENTRAL NERVOUS SYSTEM
Intracranial mass
Hemorrhage
Residual after brain injury
Quadriplegia (dysautonomia)
Sleep disordered breathing

ANCA, Antineutrophil cytoplasmic antibody.

Table 494.3 Conditions Associated with Transient or Intermittent Hypertension in Children

RENAL
Acute postinfectious glomerulonephritis
Henoch-Schönlein purpura with nephritis
Hemolytic-uremic syndrome
Acute kidney injury
After renal transplantation (immediately and during episodes of rejection)
Hypervolemia
Pyelonephritis
Renal trauma
Leukemic infiltration of the kidney
DRUGS AND POISONS
Cocaine
Oral contraceptives
Sympathomimetic agents
Amphetamines
Phencyclidine
Corticosteroids and adrenocorticotropic hormone
Cyclosporine, sirolimus, or tacrolimus treatment after transplantation
Licorice (glycyrrhizic acid)
Lead, mercury, cadmium, thallium
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
Vitamin D intoxication
Ma-huang
CENTRAL AND AUTONOMIC NERVOUS SYSTEM
Increased intracranial pressure
Guillain-Barré syndrome
Burns
Familial dysautonomia
Stevens-Johnson syndrome
Posterior fossa lesions
Porphyria
Poliomyelitis
Encephalitis
Spinal cord injury (autonomic storm)
MISCELLANEOUS
Preeclampsia
Pain, anxiety
Hypercalcemia
After coarctation repair
White blood cell transfusion
Extracorporeal membrane oxygenation

associated with umbilical artery catheterization, renal artery thrombosis, or bronchopulmonary dysplasia. Hypertension during early childhood may be caused by kidney disease, coarctation of the aorta, endocrine disorders, or medications.

Kidney disease (e.g., acute or chronic glomerulonephritis, reflux or obstructive nephropathy, hemolytic-uremic syndrome, polycystic kidney disease, congenital anomalies of the kidney and urinary tract) and **renovascular hypertension** account for approximately 90% of children with secondary hypertension. Parenchymal kidney disease and renal artery stenosis lead to water and sodium retention thought to be, in part, secondary to increased renin secretion. **Coarctation of the aorta** must always be considered, even in adolescents. **Obstructive sleep apnea** is associated with hypertension in children, and patients with hypertension and symptoms of obstructive sleep apnea (snoring, daytime somnolence, insomnia, pauses in breathing) should be referred for polysomnography. Several **endocrinopathies** are associated with hypertension, usually those involving the thyroid, parathyroid, and adrenal glands. Systolic hypertension and tachycardia are common in hyperthyroidism; DBP is not usually elevated. **Hypercalcemia**, whether secondary to hyperparathyroidism or other causes, often results in mild elevation in BP because of an increase in vascular tone. **Adrenocortical disorders** (e.g., aldosterone-secreting tumors, sodium-retaining congenital adrenal hyperplasia, Cushing syndrome) may produce hypertension in patients with increased mineralocorticoid secretion. It is important to consider conditions associated with real or apparent **mineralocorticoid excess** and thus a *suppressed* renin level (with or without hypokalemia) form of secondary hypertension (Table 494.4 and Fig. 494.1). **Pheochromocytomas** are catecholamine-secreting tumors that give rise to hypertension because of the cardiac and peripheral vascular effects of epinephrine and norepinephrine. Children with pheochromocytoma usually have sustained rather than the intermittent or exercise-induced hypertension seen in adults. Pheochromocytoma develops in approximately 5% of patients with neurofibromatosis and can also be seen in certain genetic disorders such as von Hippel-Lindau disease. Rarely, secondary hypertension can be caused by **pseudohyperaldosteronism**, which leads to elevated BP in the face of a suppressed renin level. Such disorders include Liddle syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism. Altered sympathetic tone can be responsible for acute or intermittent elevation of BP in children with Guillain-Barré syndrome, poliomyelitis, burns, and Stevens-Johnson syndrome. Intracranial lesions also affect sympathetic outflow from the central nervous system.

A number of **drugs of misuse**, **therapeutic agents**, and **toxins** may cause hypertension (Table 494.5). Cocaine may provoke a rapid increase in BP and can result in seizures or intracranial hemorrhage. Phencyclidine causes transient hypertension that may become persistent in chronic abusers. Tobacco use may also increase BP. Sympathomimetic agents used as nasal decongestants, appetite suppressants, and stimulants for attention-deficit disorder produce peripheral vasoconstriction and varying degrees of cardiac stimulation. Individuals vary in their susceptibility to these effects. Oral contraceptives should be suspected as a contributor to elevated BP in adolescent girls, although the incidence is lower with the use of low-estrogen preparations. Immunosuppressant agents such as cyclosporine and tacrolimus cause hypertension in organ transplant recipients, and the effect is exacerbated by the coadministration of corticosteroids. BP may be elevated in patients with poisoning by a heavy metal (lead, cadmium, mercury).

In older school-age children and adolescents, **primary hypertension** becomes increasingly common. These patients often are overweight, have a strong family history of hypertension, and have BP values at, or only slightly above, the 95th percentile for age. Isolated systolic hypertension is also more consistent with primary hypertension, whereas diastolic hypertension may suggest a secondary cause. The cause of primary hypertension is likely to be multifactorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system overactivity, and insulin resistance have been implicated in this disorder. Elevated uric acid levels may play a role in the pathophysiology of primary hypertension, and elevated uric acid levels have been associated with higher SBP and DBP in children. Proof-of-concept studies have confirmed that lowering of uric acid levels results in lower BP in overweight youth with hypertension or prehypertension. Some children and adolescents demonstrate *salt-sensitive hypertension*. This is more common in children with primary hypertension and may be ameliorated by weight loss and sodium restriction.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents. When subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and BP than do children of normotensive parents. Similarly, some children of hypertensive parents may excrete higher levels of urinary catecholamine metabolites or may respond to sodium loading with greater weight gain and increases in BP than do those without a family history of hypertension. The abnormal responses in children with affected parents tend to be greater in the Black population than among White individuals.

Table 494.4 Clinical Findings in Patients with Mineralocorticoid Excess

CONDITION	INVOLVED GENE	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	*CYP11B1* (autosomal recessive)	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17α-hydroxylase deficiency	*CYP17A1* (autosomal recessive)	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	*HSD11β;* deficiency of 11β hydroxysteroid dehydrogenase (autosomal recessive)	Growth stunting/short stature, nephrocalcinosis, hypokalemia, low renin, hypoaldosteronism
Liddle syndrome	*SCNN1A* *SCNN1B* *SCNN1G* (autosomal dominant)	Severe hypertension, hypokalemia, metabolic alkalosis, muscle weakness
Geller syndrome (exacerbated by pregnancy)	GOF variant in mineralocorticoid receptor gene *NR3C2* (autosomal dominant)	Early onset of hypertension (before age 20 yr), exacerbated in pregnancy: hypokalemia, low renin
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Chimeric gene with ACTH responsive promoter of 11β hydroxylase fused with aldosterone synthase gene (autosomal dominant)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypoaldosteronism type 2 (Gordon syndrome)	*WNK1* *WNK4* *KLHL3* *CUL3* (autosomal dominant)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure, low renin
Glucocorticoid resistance (children) (Chrousos syndrome)	*NR3C1* (autosomal dominant or sporadic)	Ambiguous genitalia, precocious puberty; women may have androgen excess: acne, excessive hair, oligo/anovulation, infertility

CAH, Congenital adrenal hyperplasia; GOF, gain of function.
Modified from Melcescu E, Phillips J, Moll G, et al. 11 Beta-hydroxylase deficiency and other syndromes of mineralocorticoid excess as a rare cause of endocrine hypertension. *Horm Metab Res.* 2012;44:867–878, Table 1.

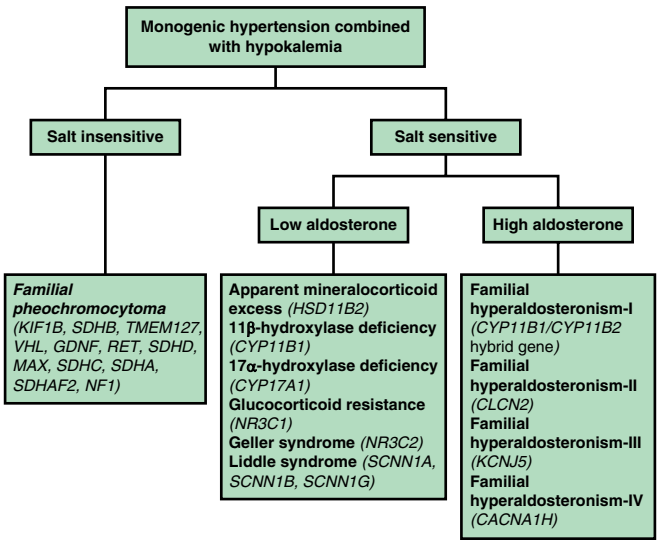

Fig. 494.1 Algorithm showing the overall categorization of monogenic hypertension combined with hypokalemia. Involved genes are italicized and in parentheses. *(From Lu YT, Fan P, Zhang D, et al. Overview of monogenic forms of hypertension combined with hypokalemia. Frontiers Pediatr. 2021;8:Article 543309, Fig. 1.)*

CLINICAL MANIFESTATIONS

Children and adolescents with primary hypertension are usually asymptomatic; the BP elevation is usually mild and is detected during a routine examination or evaluation before athletic participation. These children may also be obese. Children with secondary hypertension can have BP elevations ranging from mild to severe. Unless the BP has been sustained or is rising rapidly, hypertension does not usually produce symptoms. Therefore clinical manifestations may instead reflect the underlying disease process, such as growth failure in children with CKD. Children and adolescents with **acute severe hypertension**, in contrast, present with BP elevation well above stage 2 hypertension and severe symptoms that may represent acute target-organ injury.

Subclinical hypertensive **target-organ injury** is a common clinical manifestation in children with primary hypertension. Using echocardiography with pediatric normative data, left ventricular hypertrophy is detected in up to 40% of hypertensive children. Other markers of target-organ damage that have been demonstrated in hypertensive children include hypertensive retinopathy, increased carotid intima-to-media thickness, and increased vascular stiffness. Studies have shown that children with hypertension perform worse on tests of neurocognition than normotensive children and that these test results improve with successful treatment of hypertension. Target-organ effects of increased BP can be detected in adolescents even at BP levels below what is currently considered hypertensive.

Table 494.5 Drugs That May Elevate Blood Pressure

CLASS	DRUG
Antiinflammatory agents	COX-2 inhibitors (celecoxib) NSAIDs (ibuprofen, ketorolac)
Corticosteroids	Prednisone Hydrocortisone Dexamethasone
CNS stimulants	ADHD medications (methylphenidate, atomoxetine) Caffeine
Drugs of misuse	Amphetamines Cocaine MDMA Phencyclidine Tobacco
Estrogen- and progesterone-containing agents	HRT Oral contraceptives
Heavy metals	Cadmium Lead Mercury
Immunosuppressive agents	Cyclosporine Sirolimus Tacrolimus
Psychiatric agents	SNRI SSRI Tricyclic antidepressants
Supplements	Ephedra Guarana Ginseng Licorice St. John's wort Ma-huang
Sympathomimetic agents	Appetite suppressants Decongestants

COX-2, Cyclooxygenase-2; NSAID, nonsteroidal antiinflammatory drug; ADHD, attention-deficit/hyperactivity disorder; HRT, hormone replacement therapy; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

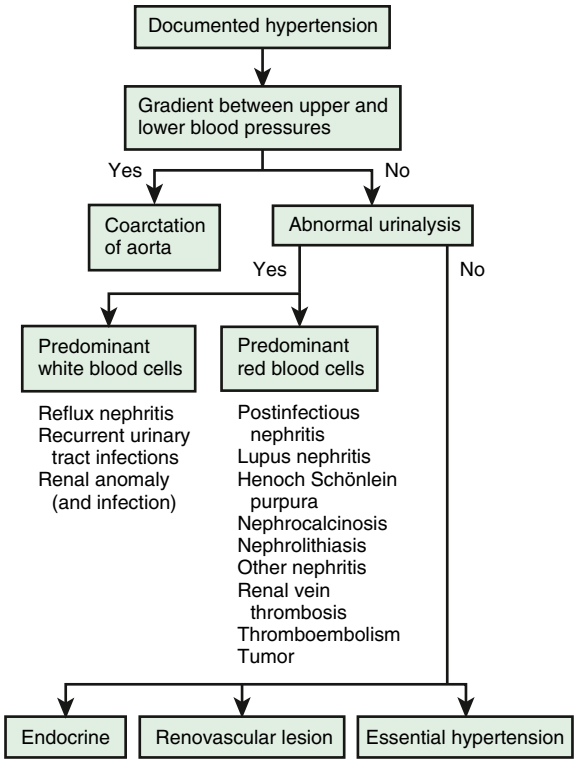

Fig. 494.2 Initial diagnostic algorithm in the evaluation of hypertension. *(From Kliegman RM, Greenbaum LA, Lye PS, eds. Practical Strategies in Pediatric Diagnosis and Therapy, 2nd ed. Philadelphia: Elsevier; 2004, p. 222.)*

DIAGNOSIS

The first step in diagnosing hypertension is recognition of elevated BP. BP readings taken in the office should be compared to normative BP tables (see 2017 AAP guidelines), indexed by height and sex, to ensure that the patient is normotensive. Multiple studies have shown substantial underrecognition of hypertension in children and adolescents, with less than half of elevated BP readings recognized, and even fewer with appropriate follow-up. This may be related to the complexity of the normative tables, although other factors such as provider experience and the presence or absence of obesity have also been shown to affect recognition of elevated BP readings. In addition to use of the simplified screening table found in the 2017 AAP guideline (see Table 494.1), this issue could also be overcome by building alerts into the electronic medical record. Elevated office BP readings should be confirmed using ABPM to identify children with white coat hypertension, who may not require further evaluation. This may require referral to an appropriate subspecialist.

Once the diagnosis of sustained hypertension is made, the evaluation should be directed toward uncovering potential underlying causes of the hypertension (Fig. 494.2), evaluating for comorbidities, and screening for evidence of target-organ damage. The extent of the evaluation for underlying causes of hypertension depends on the type of hypertension that is suspected. An extensive evaluation may be necessary when secondary hypertension is a strong consideration, such as in younger children, or in older children with severe, symptomatic hypertension. Alternatively, school-age children and adolescents with overweight/obesity and a family history of hypertension who have mild elevations of BP may only need limited testing.

In all patients, a careful **history** and **physical examination** are warranted. Birth history should be documented to screen for prematurity and other perinatal events that may affect later BP. A family history for metabolic disease, kidney disease, early cardiovascular events, and other forms of secondary hypertension should be obtained. Growth parameters should be determined to detect evidence of chronic disease. BP should be obtained in all four extremities to detect coarctation (thoracic or abdominal) of the aorta. Table 494.6 identifies other features of the physical examination that may provide evidence of an underlying cause of hypertension. Unless the history and physical examination suggest another cause, children with confirmed hypertension should have an evaluation to detect kidney disease, including urinalysis, electrolytes, blood urea nitrogen, creatinine, and complete blood count. Standard renal ultrasound should be considered in patients with a higher suspicion of secondary hypertension to assess for discrepancies in kidney size, structural abnormalities, and other potential causes of hypertension. Table 494.7 provides a more complete list of studies to consider in the clinical evaluation of a child with confirmed hypertension. Measuring serum potassium is essential because hypokalemia may be present in renovascular hypertension and many monogenic forms of hypertension (including Liddle syndrome, glucocorticoid remedial aldosteronism, and apparent mineralocorticoid excess), whereas hyperkalemia may be seen in Gordon syndrome (see Fig. 494.1). Hypokalemia may also be seen with a pheochromocytoma.

Renovascular hypertension is often associated with other diseases but may be isolated (Table 494.8). Magnetic resonance (MR) or computed tomography (CT) angiography can reveal renal artery stenosis, but formal intraarterial angiography may be needed to detect intrarenal vascular stenoses (Fig. 494.3) and in infants and young children, in whom noninvasive imaging techniques often are not helpful because of small vessel size. Doppler renal ultrasonography is of similar limited utility

Table 494.6 Physical Examination Findings in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, upturned nose, short stature, cognitive impairment	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep-disordered breathing
Webbed neck	Turner syndrome
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia–associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
Jaundice	Alagille arteriohepatic dysplasia
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome (hypokalemic low renin hypertension)
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia (11β- or 17α-hydroxylase deficiencies)
SKELETAL	
Short metacarpal (fourth, fifth) bones, short stature	Autosomal dominant hypertension with brachydactyly (Bilginturan disease)

Table 494.7 Clinical Evaluation of Confirmed Hypertension

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥90th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with signs of chronic kidney disease
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with signs or symptoms concerning for secondary cause of hypertension
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th to 94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs
Polysomnography	Identify sleep-disordered breathing	History of loud, frequent snoring, or daytime somnolence
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th to 94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th to 94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	All children with persistent BP ≥95th percentile
Renovascular imaging Magnetic resonance or CT angiography	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Arteriography: digital subtraction or classic		
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Patients with signs and symptoms concerning for pheochromocytoma

*Comorbid risk factors also include diabetes mellitus and kidney disease.
R/O, Rule out.
From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 4th Report):562.

in children because of poor patient cooperation, imaging difficulties related to obesity, and operator inexperience. Doppler renal ultrasonography has a sensitivity of approximately 60–65% in patients with renovascular disease; specificity is 95%. CT angiography has a sensitivity and specificity of 88% and 81%, respectively, compared to 80% and 63% for MR angiography. *Doppler ultrasonography is not recommended when screening for renovascular hypertension in the 2017 AAP guideline except in selected patients.*

The presence of primary hypertension often clusters with other risk factors. All hypertensive children should be screened for comorbidities that may increase cardiovascular risk, including dyslipidemia and glucose intolerance. A nonfasting lipid panel is usually sufficient to screen for dyslipidemia but should be followed up by a fasting panel if abnormal. Similarly, a random fasting glucose level may be obtained initially but will need to be followed up with a fasting level if abnormal. In addition, a sleep history should be obtained in children with confirmed hypertension to screen for **sleep-disordered breathing**, an entity that is associated with high BP, particularly in overweight children. Patients with symptoms of sleep-disordered breathing should be referred to a sleep specialist for evaluation.

Left ventricular hypertrophy (LVH) is the most common manifestation of target-organ damage in hypertensive children. Left ventricular (LV) mass measurements should be indexed to height to account for the effect of body size and body surface area (BSA). LVH is defined as LV mass >51 g/m 2.7 in those 8 years of age and older, or LV mass >115 g/BSA for boys and >95 g/BSA for females <8 years of age. According to the 2017 AAP guideline, echocardiography should be obtained when treatment with antihypertensive medications is being considered.

PREVENTION

Prevention of high BP may be viewed as part of the prevention of cardiovascular disease and stroke, the leading cause of death in adults in the United States. Other risk factors for cardiovascular disease include

Table 494.8 Causes of Renovascular Hypertension in Children

Fibromuscular dysplasia
Syndromic causes
Neurofibromatosis type 1
Tuberous sclerosis
Williams syndrome
Marfan syndrome
Other syndromes
Vasculitis
Takayasu arteritis (disease)
Polyarteritis nodosa
Kawasaki disease
Other systemic vasculitides
Extrinsic compression
Neuroblastoma
Wilms tumor
Other tumors
Other causes
Radiation
Umbilical artery catheterization
Trauma
Congenital rubella syndrome
Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al. Renovascular hypertension in children. *Lancet*. 2008;371:1453–1463, Panel 1.

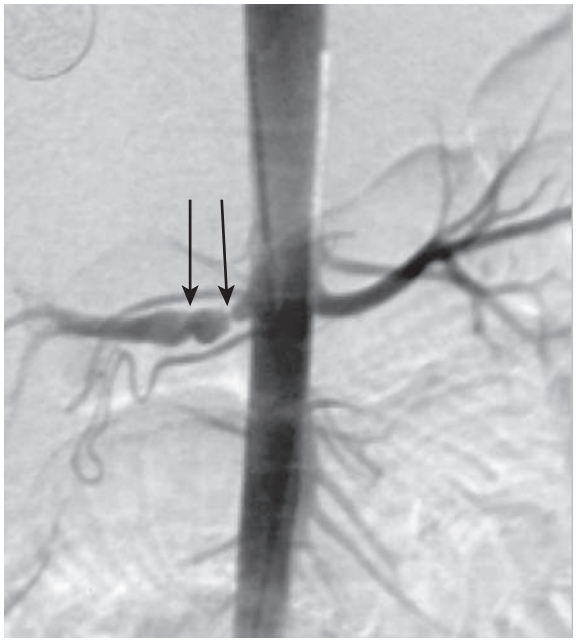

Fig. 494.3 Renal angiogram in 7-yr-old child with hypertension. Right renal artery is visible with a string-of-beads appearance characteristic of fibromuscular dysplasia *(arrows)*. The aorta and left renal artery appear normal. *(From Tullus K, Brennan E, Hamilton G, et al. Renovascular hypertension in children. Lancet. 2008;371:1453–1463, Fig 1.)*

obesity, elevated serum cholesterol levels, high dietary sodium intake, and a sedentary lifestyle, as well as alcohol and tobacco use. The increase in arterial wall rigidity and blood viscosity that is associated with exposure to the components of tobacco may exacerbate hypertension. Public health, population-based approaches to prevention of primary hypertension in both adults and children include a reduction in obesity, reduced sodium intake, avoidance of tobacco intake, and an increase in physical activity through school- and community-based programs.

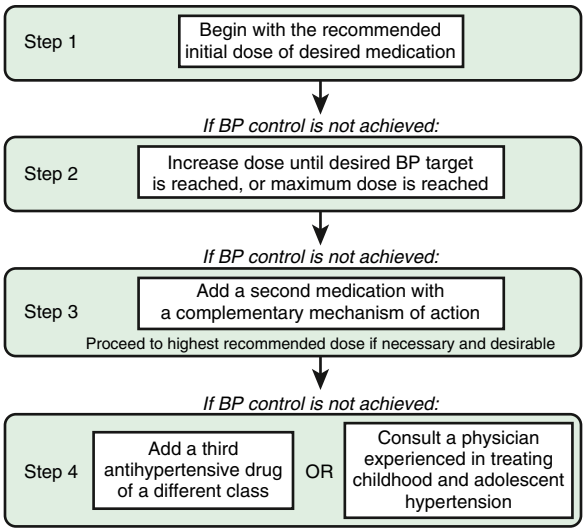

Fig. 494.4 Stepped-care approach to antihypertensive therapy in children and adolescents. BP, Blood pressure. *(From Flynn JT, Daniels SR. Pharmacologic treatment of hypertension in children and adolescents. J Pediatr. 2006;149:746–754, Fig 2.)*

TREATMENT

The mainstay of therapy for children with asymptomatic mild hypertension without evidence of target-organ damage is therapeutic **lifestyle modification** with dietary changes and regular exercise. **Weight loss** is the primary therapy in obesity-related hypertension. It is recommended that all hypertensive children have a diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy and reduced in sodium. The **DASH** (Dietary Approaches to Stop Hypertension) diet has been suggested as a nutritional approach to prevent or treat hypertension (www.dashdiet.org). The diet focuses on lowering sodium intake and increasing potassium-, calcium-, and magnesium-containing foods, such as six to eight servings of whole grains, four to five servings of fruits, and four to five servings of vegetables per day and low-fat dairy foods. For adults, the standard DASH diet contains 2,300 mg of sodium (also recommended by the American Heart Association) and the low-sodium DASH diet recommends up to 1,500 mg of sodium per day. Studies suggest that although the DASH diet has potential beneficial effects on blood pressure, adherence to the diet remains low among adolescents. In addition, regular aerobic physical activity for at least 30-60 minutes on most days along with a reduction of sedentary activities to <2 hours a day is recommended.

Indications for **pharmacologic therapy** include symptomatic hypertension, stage 2 hypertension without a modifiable risk factor, hypertension in patients with comorbidities such as diabetes (types 1 and 2) or CKD, and persistent hypertension despite nonpharmacologic measures. When indicated, antihypertensive medication should be initiated as a single agent at a low dose (Fig. 494.4). The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached, or if the child develops side effects, a second drug from a different class can be added.

Most classes of antihypertensive agents have been shown to reduce blood pressure in children and adolescents, although no data exist demonstrating one class to be superior. Per the 2017 AAP practice care guidelines, ACEIs, ARBs, thiazide diuretics, and calcium channel blockers are considered acceptable initial agents for use in children. The choice of antihypertensive agent for a patient should be tailored to the etiology of that patient's hypertension whenever possible. Table 494.9 gives recommended dosing information for antihypertensive agents in children and adolescents.

Table 494.9 Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone	25 mg/day	qd-bid	100 mg/day
	Spironolactone†	1 mg/kg/day	qd-bid	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril†	0.2 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Captopril†	0.5 mg/kg/dose (0.05 mg/kg/dose in infants)	tid	6 mg/kg/day up to 450 mg/day
	Enalapril†	0.08 mg/kg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Lisinopril†	0.07 mg/kg/day up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5-10 mg/day	qd	80 mg/day
	Ramipril	1.6 mg/m^2/day	qd	6 mg/m^2/day up to 10 mg/day
Angiotensin receptor blockers	Candesartan	1-6 yr: 0.2 mg/kg/day 6-17 yr: <50 kg 4-8 mg qd >50 kg 8-16 mg qd	qd	1-6 yr: 0.4 mg/kg up to 4 mg/day 6-17 yr: <50 kg: 16 mg qd >50 kg: 32 mg qd
	Losartan†	0.75 mg/kg/day up to 50 mg/day	qd	1.4 mg/kg/day up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd	qd	20 to <35 kg: 20 mg qd ≥35 kg: 40 mg qd
	Valsartan†	6-17 yr: 1.3 mg/kg/day up to 40 mg/day	qd	6-17 yr: 2.7 mg/kg/day up to 160 mg/day
α- and β-adrenergic antagonists	Labetalol†	2-3 mg/kg/day	bid	10-12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 6.25 mg bid	bid	0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol†	0.5-1 mg/kg/day	qd-bid	2 mg/kg/day up to 100 mg/day
	Bisoprolol/HCTZ	2.5/6.25 mg/day	qd	10/6.25 mg/day
	Metoprolol	1-2 mg/kg/day	bid	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	bid-tid	8 mg/kg/day up to 640 mg/day
Calcium channel blockers	Amlodipine†	1-5 yr: 0.1 mg/kg/day ≥6 yr: 2.5 mg/day	qd	1-5 yr: 0.6 mg/kg/day up to 5 mg/day ≥6 yr: 10 mg/day
	Felodipine	2.5 mg/day	qd	10 mg/day
	Isradipine†	0.05-0.15 mg/kg/dose	tid-qid	0.6 mg/kg/day up to 10 mg/day
	Extended-release nifedipine	0.2-0.5 mg/kg/day	qd-bid	3 mg/kg/day up to 120 mg/day
Central α-agonist	Clonidine†	5-10 μg/kg/day	bid-tid	25 μg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5-10 mg/day	qd	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	qd	2 mg/kg/day up to 50 mg/day
	Chlorothiazide	10 mg/kg/day	bid	20 mg/kg/day up to 375 mg/day
	Furosemide	0.5-2.0 mg/kg/dose	qd-bid	6 mg/kg/day
	HCTZ	0.5-1 mg/kg/day	qd	3 mg/kg/day up to 37.5 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	tid-qid	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1-0.2 mg/kg/day	bid-tid	1 mg/kg/day up to 50 mg/day

*The maximum recommended adult dose should never be exceeded.
†Information on preparation of a stable extemporaneous suspension is available for these agents.
bid, Twice daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.
Adapted from Flynn JT. Management of hypertension in the young: role of antihypertensive medications. *J Cardiovasc Pharmacol*. 2011;58(2):111–120.

There have been changes in the recommended BP goals for the treatment of hypertension in children and adolescents. Data from the SPRINT (SBP intervention) trial group suggests that stricter goals (SBP goal of 120 vs 140 mm Hg) improve cardiovascular outcomes in adults. In children with CKD, the ESCAPE (Effects of Strict BP Control and Angiotensin-Converting Enzyme Inhibition on the Progress of Chronic Renal Failure in Pediatric Patients) trial group showed slower progression of CKD if the 24-hour MAP was kept below the 50th percentile on ABPM compared to the 50th to 95th percentile. It is now recommended that treatment achieve BP <90th percentile for age or <130/80 mm Hg, whichever is lower. A lower goal based on ABPM (24-hour MAP <50th percentile) is recommended for children and adolescents with CKD. ACEIs or ARBs should be used for children with diabetes and microalbuminuria or proteinuric kidney disease.

Acute severe hypertension, sometimes referred to as *accelerated hypertension* or *hypertensive crisis*, is defined as severe hypertension (often with BP values well in excess of stage 2 hypertension) accompanied by symptoms such as headache, dizziness, or nausea/

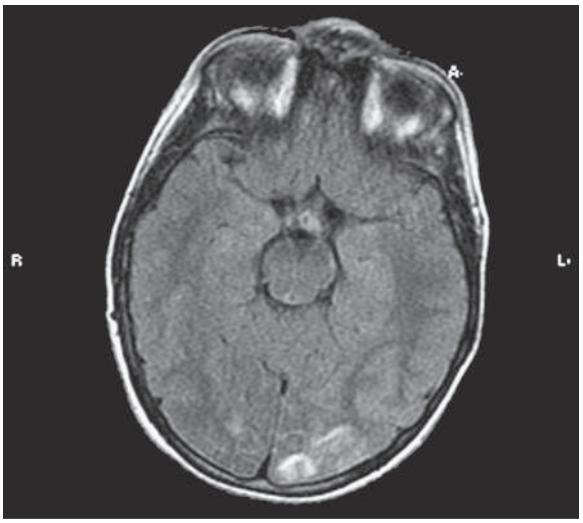

Fig. 494.5 MRI of the brain of a 6-yr-old child with end-stage kidney disease and hypertensive encephalopathy (i.e., posterior reversible leukoencephalopathy syndrome). Bilateral occipital high signal intensity is more pronounced on the left side. *(From Daroff RB, Fenichel GM, Jankovic J, et al., eds. Bradley's Neurology in Clinical Practice, 6th ed. Philadelphia: Saunders; 2012: Fig. 49B.4, p. 924.)*

vomiting, and in more severe cases, retinopathy, encephalopathy, cardiac failure, acute kidney injury, and seizures. These situations have also been described as *hypertensive urgency* and *hypertensive emergency,* respectively. This nomenclature can lead to confusion because there is often no absolute distinction between the two situations, and treatment will often depend on clinical judgment. *Hypertensive encephalopathy* (generalized or posterior reversible encephalopathy syndrome) is suggested by the presence of headache, vomiting, temperature elevation, visual disturbances, ataxia, depressed level of consciousness, imaging abnormalities, and seizures (Fig. 494.5); it is one of the more common presentations of acute severe hypertension in children and adolescents. Acute severe hypertension may also manifest with decreased vision (cortical blindness) and papilledema, congestive heart failure, or accelerated deterioration of kidney function.

For patients with acute severe hypertension and life-threatening symptoms, intensive care unit (ICU) admission and intravenous (IV) drug infusion are indicated so that decreases in BP can be carefully monitored and titrated (Table 494.10). Ideally, arterial lines should be used for continuous BP monitoring; if this is not available, oscillometric devices can be used for frequent/repeated BP measurement. Drug choices include labetalol, nicardipine, and sodium nitroprusside. Because too rapid a reduction in BP may interfere with adequate organ perfusion, a stepwise reduction in pressure should be planned. In general, BP should be reduced by

Table 494.10 Antihypertensive Drugs for Management of Severe Hypertension in Children Age 1-17 Years

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 μg/kg/min	IV infusion	Very short acting—constant infusion preferred; may cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.4 mg/kg/dose	IV, IM	Should be given every 4 hr when given IV bolus
Labetalol	α- and β-Adrenergic blocker	Bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose Infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 μg/kg up to 2 mg/dose Infusion: 0.5-4 μg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5-10 μg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure or coadminister with sodium thiosulfate
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Fenoldopam	Dopamine receptor agonist	0.2-0.8 μg/kg/min	IV infusion	Produced modest reductions in blood pressure in a pediatric clinical trial in patients up to age 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose, up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.15 mg/kg/dose, up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose, up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

IM, intramuscular; IV, intravenous; PO, oral.
Adapted from Flynn JT, Tullus K. Correction to severe hypertension in children and adolescents: pathophysiology and treatment. *Pediatr Nephrol.* 2012;27(3):503–504.

no more than 25% of the planned reduction over the first 8 hours, with a gradual normalization of BPs over the next 24-48 hours. For patients with less severe symptoms, such as headache or nausea/vomiting, oral medications such as clonidine or isradipine can be used if the patient can tolerate oral medications. Short-acting IV medications such as hydralazine or labetalol are acceptable if the patient cannot take oral drugs.

Treatment of secondary hypertension must also focus on the underlying disease, such as CKD, hyperthyroidism, pheochromocytoma, coarctation of the aorta, or renovascular hypertension. The treatment of renovascular hypertension includes antihypertensive medications, angioplasty, or surgery. If bilateral renovascular hypertension or renovascular disease in a solitary kidney is suspected, drugs acting on the RAAS are usually contraindicated because they may reduce glomerular filtration rate and lead to acute kidney injury.

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